UNIVERSITAT POLITÈCNICA DE VALÈNCIA

How do cooperation and scientific research influence drug development? The case of cancer disease

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Abstract

Over 90% of clinical trials for cancer disease drugs fail. It is therefore necessary to increase understanding about the factors that increase the success of drug development. In the present thesis, this issue is addressed from the perspective of Innovation Studies. To this end, 103 articles related to clinical trials, published in innovation journals (1984–2021), are revised systematically. The existing findings are summarised, the studies are classified into categories and some suggestions for potential theoretical and methodological advances in Innovation Studies are provided. It is found that product life cycle and user innovation theories should be applied in future research to improve understanding about drug development. Further use of causal, regression and mixed-methods analysis is also recommended, especially related to the topics of commercialisation, knowledge transfer and institutional frameworks, along with a better use of machine learning and programming languages with regards to data gathering computer tools. Based on the research gaps identified in the literature review, an exploration is made of the role of radicalness, network formation, and the basicness and scientific impact of research on the success of drug development through clinical trials. The results show that a greater degree of radicalness is less likely to achieve success. The relationship between network density and success rate follows an inverted U-shape. In denser cooperation networks, radical organisations have a greater possibility of achieving success. Radical drug development involves organisations taking more risks, which results in more failures; however, an effective way of increasing the success rate of radical drug development is by promoting cooperation network density. Applied research encourages organisations to engage in drug development, and basic research is useful for increasing the success rate of drug development. Nevertheless, the applied research of cooperators also increases the success rate through network spillovers. The scientific impact of research plays a positive role

in both the engagement and success of drug development, directly and through network spillovers. This thesis provides some insights to increase the success rate of drug development for medical organisations and policymakers through science, cooperation and innovation strategies.

Keywords: innovation, drug development, clinical trials, radicalness, cooperation, networks, scientific research, basicness, scientific impact, spillover effect.

Resumen

Más del 90 por ciento de los ensayos clínicos de medicamentos contra el cáncer fracasan. Por tanto, es necesario mejorar el conocimiento sobre los factores que aumentan el éxito del desarrollo de medicamentos. En esta tesis, se aborda esta cuestión desde la perspectiva de los Estudios de Innovación. Para ello, se revisa sistemáticamente 103 artículos relacionados con ensayos clínicos, publicados en revistas de innovación (1984-2021). Así se logra sintetizar los hallazgos existentes, clasificar los estudios por categorías y proporcionar algunas sugerencias teóricas y metodológicas para trabajos futuros. Se encuentra que las teorías del ciclo de vida del producto y de la innovación del usuario deberían ser aplicadas en la investigación futura para mejorar la compresión sobre el desarrollo de medicamentos. Se recomienda un mayor uso de los análisis causales, de regresión y de metodologías mixtas, especialmente en relación con los temas de la comercialización, la transferencia de conocimiento y los marcos institucionales, así como un mejor uso del aprendizaje automático y los lenguajes de programación por lo que se refiere a las herramientas informáticas de recogida de datos. De acuerdo con las lagunas de investigación identificadas en la revisión de la literatura, se explora el papel de la radicalidad, la formación de redes, la naturaleza básica y el impacto científico de la investigación en el éxito del desarrollo de fármacos a través de ensayos clínicos. Los resultados muestran que un mayor grado de radicalidad es menos susceptible de conducir al éxito. La relación entre densidad de la red y la tasa de éxito sigue una forma de U invertida. En redes de cooperación más densas, las organizaciones radicales tienen más posibilidades de éxito. El desarrollo radical de medicamentos implica que las organizaciones asuman más riesgos, lo que da lugar a más fracasos; sin embargo, una manera efectiva de incrementar la tasa de éxito del desarrollo radical de medicamentos es mediante la promoción de la densidad de las redes de cooperación. La investigación aplicada facilita que las organizaciones se involucren

en el desarrollo de medicamentos, y la investigación básica es útil para incrementar la tasa de éxito del desarrollo de medicamentos. No obstante, la investigación aplicada de los cooperantes también incrementa la tasa de éxito a través de los efectos desbordamiento de la red. El impacto científico de la investigación juega un papel positivo tanto en involucrarse en el desarrollo de medicamentos como en conducirlo al éxito, directamente y través de los efectos desbordamiento de la red. Esta tesis proporciona algunas ideas para aumentar la tasa de éxito del desarrollo de medicamentos para organizaciones médicas y formuladores de políticas a través de estrategias de ciencia, cooperación e innovación.

Palabras clave: innovación, desarrollo de medicamentos, ensayos clínicos, radicalidad, cooperación, redes, investigación científica, naturaleza básica de la investigación, impacto científico, efecto desbordamiento.

Resum

Més del 90 per cent dels assajos clínics de fàrmacs contra el càncer fracassen. Per tant, és necessari millorar el coneixement sobre els factors que augmenten l'èxit del desenvolupament de fàrmacs. En aquesta tesi, s'aborda aquesta qüestió des de la perspectiva dels Estudis d'Innovació. Per a això, es revisa sistemàticament 103 articles relacionats amb assajos clínics, publicats en revistes d'innovació (1984-2021). Així s'aconsegueix sintetitzar les troballes existents, classificar els estudis per categories i proporcionar alguns suggeriments teòrics i metodològics per a treballs futurs. Es troba que les teories del cicle de vida del producte i de la innovació de l'usuari haurien de ser aplicades en la investigació futura per a millorar la compressió sobre el desenvolupament de fàrmacs. Es recomana un major ús de les anàlisis causals, de regressió i de metodologies mixtes, especialment en relació amb els temes de la comercialització, la transferència de coneixement i els marcs institucionals, així com un millor ús de l'aprenentatge automàtic i els llenguatges de programació pel que fa a les eines informàtiques de recollida de dades. D'acord amb les llacunes d'investigació identificades en la revisió de la literatura, s'explora el paper de la radicalitat, la formació de xarxes, la naturalesa bàsica i l'impacte científic de la investigació en l'èxit del desenvolupament de fàrmacs a través d'assajos clínics. Els resultats mostren que un major grau de radicalitat és menys susceptible de conduir a l'èxit. La relació entre densitat de la xarxa i la taxa d'èxit segueix una forma d'U invertida. En xarxes de cooperació més denses, les organitzacions radicals tenen més possibilitats d'èxit. El desenvolupament radical de fàrmacs implica que les organitzacions assumisquen més riscos, la qual cosa dona lloc a més fracassos; no obstant això, una manera efectiva d'incrementar la taxa d'èxit del desenvolupament radical de fàrmacs és mitjançant la promoció de la densitat de les xarxes de cooperació. La investigació aplicada facilita que les organitzacions s'involucren en el desenvolupament de fàrmacs, i la investigació bàsica és útil per a incrementar la taxa d'èxit del desenvolupament de fàrmacs. No obstant això,

la investigació aplicada dels cooperants també incrementa la taxa d'èxit a través dels efectes desbordament de la xarxa. L'impacte científic de la investigació juga un paper positiu tant a involucrar-se en el desenvolupament de fàrmacs com a conduir-lo a l'èxit, directament i través dels efectes desbordament de la xarxa. Aquesta tesi proporciona algunes idees per a augmentar la taxa d'èxit del desenvolupament de fàrmacs per a organitzacions mèdiques i formuladors de polítiques a través d'estratègies de ciència, cooperació i innovació.

Paraules clau: innovació, desenvolupament de fàrmacs, assajos clínics, radicalitat, cooperació, xarxes, investigació científica, natura bàsica de la investigació, impacte científic, efecte desbordament.

Chapter 1

Introduction

There were over 55 million human deaths worldwide in 2019, and 74% of them were caused by non-communicable diseases (WHO, 2020). Cancer is the most dangerous chronic non-communicable disease in the world, causing the death of 9.3 million people every year (WHO, 2022), and patients require effective drugs to cure it. A great many organisations are engaged in a monumental effort to find new drugs to cure cancer diseases, and innovation scholars are paying increasing attention to the analyses of the drug development process (Das et al., 2018; Belousova et al., 2020). The question of how to improve the success rate of new drugs is a major issue.

Innovation in drug development provides some opportunities to reduce patients' suffering and decrease their mortality rate. In the medical area, staying competitive also calls for medical organisations to keep pace with the speed of innovation (Moaniba et al., 2020). Innovation ensures that medical firms maintain a high performance (Feng et al., 2022). Medical firms have gradually diverted their innovation efforts in drug development from generic to original drugs to cure diseases and maintain competitive advantages (Branstetter et al., 2022). Innovation in radical technologies is a promising approach to develop more drugs to cure cancer disease (Jaffee et al., 2017).

Clinical trials, a set of tests for evaluating a medical, surgical, or behavioural intervention in vivo, are the necessary processes of medical innovation to transform a new chemical entity or biological candidate into a product. Drugs have to pass three phases of clinical trials before they can be commercialised. Clinical trials involve huge amount of monetary and time costs (Martin et al., 2017), but they rarely succeed, especially in cancer diseases (Hutchinson & Kirk, 2011; Begley & Ellis, 2012). Both industry and academic hope to improve the success rate of drug development through analysing clinical trials (Hay et al., 2014). Clinical trials present the details of how innovative ideas transfer into new products. Analysing clinical trials

helps deepen knowledge of the innovation process of new products in the medical area. Therefore, the objective of this thesis is to acquire a greater understanding of how to promote the success of drug development by analysing clinical trials in cancer disease.

This thesis is based on the compilation of three scientific studies. Chapters 2, 3 and 4 are aimed at producing individual scientific papers, each with its own introduction, results and conclusions, oriented towards being published in peer-reviewed scientific journals. They all follow a common thread, namely the study of drug development through clinical trials in the innovation area. Chapter 2 is a systematic literature review, and Chapters 3 and 4 use empirical approaches. Further details on the chapters are provided below.

Chapter 2 reviews the existing studies related to the analysis of drug development through clinical trials in innovation journals. Innovation researchers have gradually been focusing more on innovation in the medical area by analysing clinical trials. To clarify how the field of Innovation Studies has already approached the analysis of clinical trials, Chapter 2 reviews existing clinical trials-related Innovation Studies. This systematic literature review enables an overview of the development of clinical trials-related innovation studies. Clinical trials appear in five topics of Innovation Studies: commercialisation, scientific knowledge production, knowledge transfer, institutional frameworks and data gathering computer tools. This literature review demonstrates that clinical trials-related Innovation Studies are still at the primary stage and will benefit from further development.

Through the systematic literature review, some research gaps are identified regarding the complexity of drug development. For example, there is a need to deepen the role of radicalness and network formation in the success of drug development through clinical trials. Chapter 3 constitutes an attempt to address these issues. In this context, success means that the medical authorities approve the tested drugs and allow them

to enter the market; cooperation network density is defined as the degree of connections between members in a research cooperation network; and radicalness refers to the extent to which organisations develop new drugs instead of reusing existing ones. The target questions are whether more radicalness leads to greater success in drug development and whether taking part in a dense (or sparse) research network is beneficial to organisations in order to achieve success. It is found that a higher degree of radicalness decreases the success rate of organisations, and that there is an inverted U-shaped relationship between research network density and success rate. In addition, organisations whose drug development has a high degree of radicalness have a greater opportunity of achieving success in a dense network.

Another gap found in the literature review (Chapter 2) concerns the role of different characteristics of scientific research and the success of drug development. Chapter 4 analyses these relationships using a network view. Scientific research refers to the knowledge and laws to explain a natural phenomenon or human behaviour through the scientific method. The improvement of scientific research not only propels advances in innovation but also drives economic and social development (da Silva, 2021). The development of scientific research in one subject is an indicator of future innovation and advances in this subject (Gittelman & Kogut, 2013). The conducting of clinical trials, an important stage of drug development, also relies on scientific research. Due to the high risks and costs of clinical trials, researchers and organisations both hope to predict the results of clinical trials through scientific research. Chapter 4 investigates whether scientific research leads to drug development and employs a network perspective to analyse the spillover effect of scientific research on drug development in cooperation networks. An analysis is made of the effects of two characteristics of scientific research — basicness and scientific impact — on the two stages of a clinical trial: entering into clinical trials (engagement) and obtaining approval (success). The results show

that the basicness of scientific research plays a negative role on engagement in clinical trials, but a positive role on success in clinical trials. Scientific impact has a positive effect both on the engagement and success of drug development. The low basicness and high scientific research are transferred via the research cooperation network, and they increase the success rate of cooperators through network spillovers.

Finally, Chapter 5 provides conclusions and some suggested avenues for future research posed by this thesis. In summary, this thesis fulfils its objective of exploring how to promote the success of drug development, and in doing so, a number of theoretical and methodological contributions are made.

There are five theoretical contributions in this thesis. First, Chapter 2 provides some theoretical suggestions for future clinical trials-related innovation studies in four dimensions, including commercialisation, scientific knowledge production, knowledge transfer and institutional frameworks. The contributions of existing clinical trials-related innovation studies are summarised and research gaps in the existing studies are detected. These research gaps inspire some insights for possible future research. Second, evidence on the relationship between radicalness and success of drug development is given in Chapter 3. Researchers are increasingly paying attention to exploring radicalness in drug development (Sternitzke, 2010; Baba & Walsh, 2010; Kapoor & Klueter, 2015). In line with previous research, Chapter 3 finds that the degree of radicalness decreases the success rate of organisations. Third, Chapter 3 also provides evidence on the relationship between cooperation network and success of drug development. Existing studies agree that cooperation is a key factor in the success of drug development (Malik, 2011; Banerjee & Siebert, 2017), but there is still a need to investigate the role of cooperation in the success of drug development from a network perspective. Chapter 3 finds that the relationship network density and success rate follows an inverted U-shape, and that in denser networks higher radicalness provides greater opportunities for achieving success.

Fourth, Chapter 4 fills the research gap in the relationship between scientific research and the success of drug development. It provides evidence on the spillover effect of cooperators' scientific research on the success of a company's own drug development. External scientific research from cooperators is an important source of acquiring knowledge and improving drug development (Allarakhia et al., 2010; Bianchi et al., 2011), but the specific role of cooperators' scientific research on the success of drug development is not yet clear. Chapter 4 confirms that basicness has a negative spillover effect and scientific impact has a positive spillover effect on the success of drug development.

Methodologically, this thesis makes three contributions. First, data scraping is introduced to collect and match clinical trials data from different sources. Data scraping is widely used to collect information from websites (Ciechanowski et al., 2020; Ricart et al., 2020). Chapter 3 provides a method for collecting clinical trials data, improving the reliability of data matching through data scraping. Second, a method to measure the radicalness of drug development is given in Chapter 3. This measures radicalness by determining whether a given organisation tested the related drugs for the first time and then calculating the percentage of new test drugs for that organisation. Third, the study innovatively introduce spatial models to analyse the spillover effect in cooperation in Chapter 4. Spatial models are mainly applied in regional studies with geographical distance (Feng et al., 2019; Pan et al., 2020). Chapter 4 analyses cooperation networks and calculates the cooperation distance between cooperators through cooperation relationships. According to the method of applying spatial models with geographical distances, the spatial Durbin model is used to analyse the spillover effect of cooperators' scientific research on the success of drug development.

Chapter 2

What we know about clinical trials from Innovation Studies: a systematic literature review

2.1 Introduction

Innovation Studies is a multidisciplinary field of science that explores why innovation activity takes place and what factors influence innovation decisions, processes and results (Fagerberg et al., 2012). Innovation refers to implementing new ideas to improve existing (or provide new) goods and services (Schumpeter, 1934). Innovation is important for the medical industry, especially for drug development (Romasanta et al., 2020), which comprises all the activities involved in transforming a chemical entity or a biological product from a drug candidate to a product approved for sale by the appropriate regulatory authorities (Rang & Hill, 2012). A number of prior medical innovation studies have investigated knowledge assets (Rzakhanov, 2018), technological change (Wagner & Wakeman, 2016), competitive strategies (Rudy & Black, 2018), innovation cooperation (Guan & Zhao, 2013), scientific impact (Kwon et al., 2019) and regulatory policy (Kwon et al., 2022) by analysing medical innovation processes in patents and publications. In addition to patents and publications, clinical trials are also key in the innovation process of new drug development, since every new drug has to pass this stage before it is launched on the market. Exploring clinical trials in Innovation Studies is an essential step towards a better understanding of the innovation process in drug development.

The conducting of clinical trials, a set of tests to verify the safety and effectiveness of potential drugs in vivo, is a necessary step in the innovation process of new drug development. A clinical trial is a critical turning point in the development of a new drug, signifying that it is fast approaching the market and the owning organisation will attract a great deal of investments through the clinical trials (Akhondzadeh, 2016). The results of clinical trials lead to the success or failure of new drug development. The investigation of clinical trial-related Innovation Studies helps academic researchers and organisations to understand the role

such trials play in the innovation process and improve their success rate and social benefits. However, not many Innovation Studies currently exist that explore medical innovation activities through clinical trials and, as far as can be ascertained, there is presently a lack of studies summarising the research topics of clinical trials in Innovation Studies. This state of affairs has been the inspiration for making this systematic literature review of clinical trial-related Innovation Studies.

To this end, this chapter gathers existing articles on clinical trial-related Innovation Studies to make a systematic literature review. The objective of this study is to provide some suggestions for future clinical trial-related Innovation Studies. Specifically, this investigation focuses on two research questions: how can we improve the analysis of certain core topics of Innovation Studies (e.g., commercialisation, scientific knowledge production and knowledge transfer) through the analysis of clinical trials as a stage in the process of drug development (RQ1)? How can we improve the use of clinical trial data in Innovation Studies (RQ2)?

The main contributions of this study can be summarised as follows. First, it takes stock of the existing research topics and analysis methods in clinical trial-related Innovation Studies. This systematic literature review classifies five topics in clinical trial-related Innovation Studies, including commercialisation, scientific knowledge production, knowledge transfer, institutional frameworks and data gathering computer tools, and presents the subtopics in each category, which will serve as the basis for subsequent research in Innovation Studies. Second, it provides some new theoretical frameworks and new ideas on empirical developments for future research in clinical trial-related Innovation Studies.

The remainder of the study is organised as follows: Section 2.2 describes the scope of the reviewed articles; Section 2.3 presents the research topics in the reviewed articles; Section 2.4 discusses the research gaps and provides some suggestions for future research; Section 2.5 summarises the emerging trends on drug

development outside Innovation Studies; and finally, Section 2.6 provides the conclusions and details some limitations of the study.

2.2 Scope of the literature review

The literature review includes clinical trial-related articles that have been published in mainstream general innovation journals. The journals retrieved were listed in the Academic Journal Guide (AJG) 2021, which classifies and ranks business and management journals based upon peer review, editorial and expert judgements and provides statistical information relating to citations (Walker & Wood, 2021). The AJG includes a search tool, "Field", with various categories, including "Innovation", which largely corresponds to the field of Innovation Studies. There are 40 journals under the category of Innovation, as Table 2.1 shows. The search was expanded to other mainstream innovation journals according to expert judgement (one of the PhD supervisors and an external advisor). These journals are also in the AJG, but under other categories (see Table 2.1, expanded journals).[1]

Once the journals had been selected, papers were retrieved from their respective websites. The papers collected are from 1984 to 2021 with the term "clinical trial*". A total of 103 publications meet this search criterion, as presented in Table 2.1. The number of reviewed articles in *Research Policy* (6), the top innovation journal, is almost 3 times the average number of papers (2.2). Over half of the papers are from the following three journals: *Social Studies of Science* (25), *Scientometrics* (20) and *Science Technology and Human Values* (14). The reviewed articles in *Social Studies of Science* and *Science Technology and Human Values* focus on the institutional framework of innovation with qualitative analysis. In *Scientometrics*, most

[1] Other databases, such as Scopus, consider these publications to be Innovation journals, classifying them under the category of "Management of technology and innovation".

of the reviewed articles explore scientific knowledge production with quantitative analysis. There are 25 (54%) journals without any papers on clinical trial innovation, and almost half of the reviewed articles (47%) were published in the last five years of the period under study, according to Appendix Table A1, which indicates that researchers have been paying increasing attention to clinical trial-related Innovation Studies in recent years.

Table 2.1 Innovation field journals in Academic Journal Guide 2021 expanded

Journal title	AJG ranking	Nº of articles
AJG 2021 innovation journals		95
Research Policy	4*	6
Journal of Product Innovation Management	4	0
Industry and Innovation	3	0
Journal of Technology Transfer	3	2
R and D Management	3	5
Technological Forecasting and Social Change	3	5
Technovation	3	2
Creativity and Innovation Management	2	2
Innovation: Organization & Management	2	0
International Journal of Innovation Management	2	0
Journal of Engineering and Technology Management – JET-M	2	0
Journal of High Technology Management Research	2	0
Prometheus	2	1
Research Technology Management	2	1
Science and Technology Studies	2	3
Science Technology and Human Values	2	14
Scientometrics	2	20
Social Studies of Science	2	25
Structural Change and Economic Dynamics	2	0
Asian Journal of Technology Innovation	1	0
European Journal of Innovation Management	1	0
International Journal of Business Innovation and Research	1	1
International Journal of Entrepreneurship and Innovation Management	1	0
International Journal of Foresight and Innovation Policy	1	0
International Journal of Innovation and Sustainable Development	1	0
International Journal of Innovation and Technology Management	1	0
International Journal of Innovation Science	1	1
International Journal of Product Development	1	0
International Journal of Technology and Globalisation	1	0
International Journal of Technology Intelligence and Planning	1	1
International Journal of Technology Management and Sustainable Development	1	0
International Journal of Technology Transfer and Commercialisation	1	2
International Journal of Technology, Policy and Management	1	0
International Journal of the Digital Human	1	0
International Technology Management Review	1	0
Journal of Innovation and Knowledge	1	0
Journal of Innovation Economics & Management	1	3
Journal of Science and Technology Policy Management	1	0
Journal of the Knowledge Economy	1	0
Technology Innovation Management Review	1	1
Expanded journals		8
Industrial and Corporate Change [a]	3	0
Small Business Economics [b]	3	1
Economics of Innovation and New Technology [c]	2	3
Journal of Evolutionary Economics [c]	2	2
Journal of Knowledge Management [d]	2	0
Science and Public Policy [a]	2	2
SUM		103

AJG ranking indicates journal quality from 1 (low quality) to 4 (high quality).*

a Social Science; b Entrepreneurship and Small Business Management; c Economics; d Organisational Studies.

2.3 Principal topic areas

The review of the identified target articles is organised into the following principal topic areas: commercialisation, scientific knowledge production, knowledge transfer, institutional frameworks and data gathering computer tools. The first four categories relate to contents of the articles, whereas the fifth (data gathering computer tools) relates to technical aspects. Figure 2.1 displays the links between the first four topics. Scientific knowledge production overlaps with commercialisation and continuous feedback mechanisms operate between them, mainly in the form of knowledge transfer. All the stages of medical innovation with clinical trials, including scientific knowledge production, knowledge transfer and commercialisation overlap with the prevailing institutional frameworks, i.e., the systemic set of norms, regulations, cultural and ethical concerns which shape and are shaped by the innovation process. The data gathering computer tools provide some ways to retrieve information about clinical trial data.

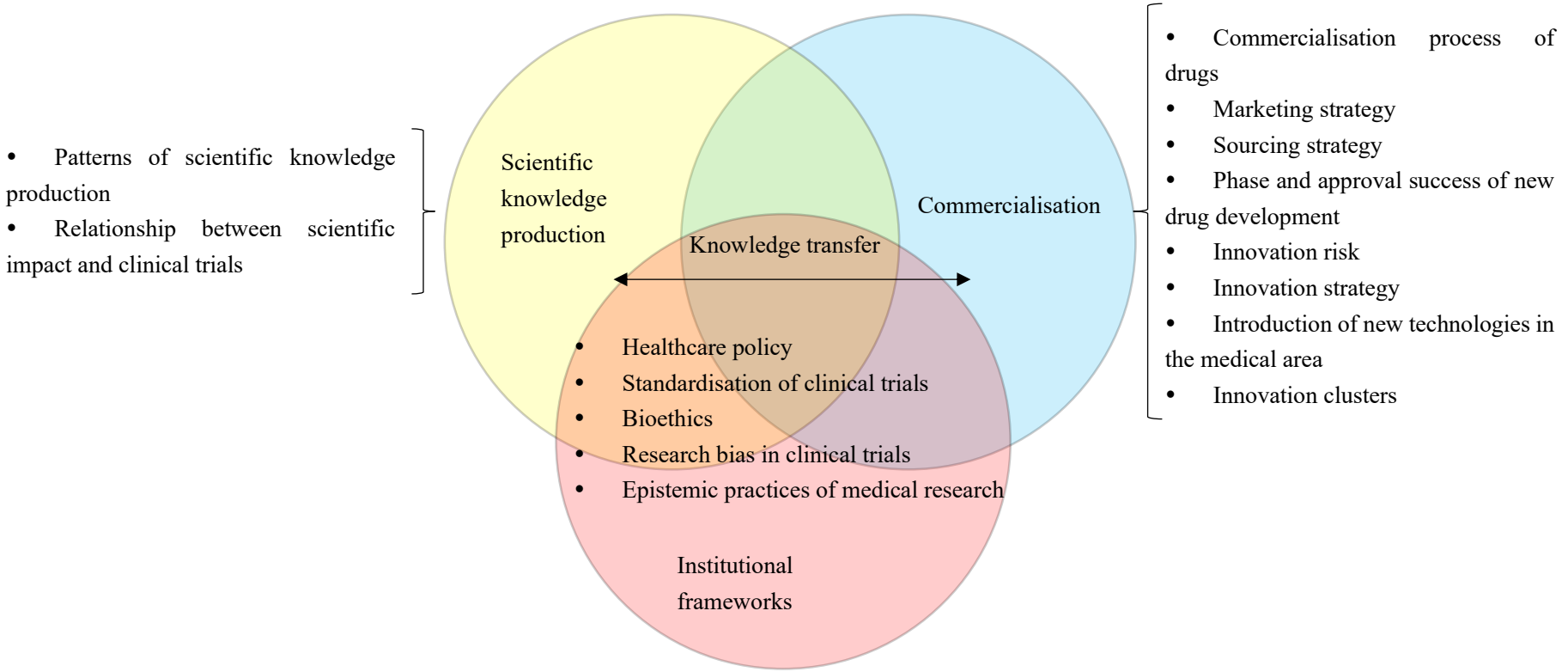


Figure 2.1 Principal topic areas of clinical trial-related Innovation Studies

Table 2.2 shows the distribution of the reviewed articles according to each topic. Most reviewed articles are on the topics of commercialisation (36%), institutional frameworks (35%) and scientific knowledge production (18%). There are only a few papers on the topics of knowledge transfer (6%) and data gathering computer tools (5%).

Table 2.2 Distribution of studies by topic area

Topic Area	Nº of studies	Percentage of studies
Commercialisation	37	36%
Scientific knowledge production	19	18%
Knowledge transfer	6	6%
Institutional frameworks	36	35%
Data gathering computer tools	5	5%
Total	103	100%

2.3.1 Commercialisation

Commercialisation is the process or cycle of introducing a new drug or treatment into the market (Anderson, 1990). The new drug or treatment has to pass clinical trials and receive approval from the government before it is launched on the market. For this reason, commercialisation is widely discussed in clinical trial-related Innovation Studies. Furthermore, the literature review found a set of subareas: commercialisation process of drugs, marketing strategy, sourcing strategy, phase and approval success of new drug development, economic performance of the new drug development, innovation risk, innovation strategy, introduction of new technologies in the medical area and innovation clusters. Below, each of these subareas is expanded upon.

Commercialisation process of drugs refers to transforming a new drug and placing it on the market,

along with the associated risks and challenges involved. The main aim for organisations in carrying out clinical trials on new drugs is to launch them on the market through commercialisation. Therefore, it is not surprising that this subtopic has also received considerable attention in the literature focused on the commercialisation of clinical trials. Kohli-Laven et al. (2021) compared the commercial processes of clinical trials between Onco type DX and MammaPrint and found that Onco type DX began with a commercial platform, which was commercialised according to the requirements of users. MammaPrint began with a breast cancer signature and established a company to commercialise it. Callagher et al. (2018) discussed the challenges in pre-clinical and clinical trials, including regulatory hurdles, rapid changes to legislation, the impact of public opinion, raising capital, maintaining cash flow and developing a pipeline of opportunities over a long period of commercialisation.

Marketing strategy refers to using product, price, distribution and promotion programmes to reach prospective consumers and convert them into customers of their drugs or medical services. Marketing strategy is a very important strategy in commercialising new drugs and treatments, and publishing positive results of clinical trials is increasingly applied as a type of marketing strategy, since marketing strategy not only transforms the perceptions of physicians but also shapes patients' willingness to receive treatment and the treatment awareness of potential patients. Thus, marketing strategy is explored in clinical trial-related Innovation Studies. Healy (2004) found that clinical trials and ghost-written scientific papers authored by celebrity researchers are becoming the marketing strategies for drugs. The portfolio of marketing strategies has created a transformation in the way diseases are diagnosed and treated, resulting in an increase of many diseases being treated by a few specific drugs. Fishman (2004) detected that academic clinical trial researchers are the keys to marketing strategies because they are the mediators between the producers (the

pharmaceutical companies) and consumers (clinicians and patients) of new drugs. The academic clinical trial researchers not only conducted clinical trial research, but also participated in some other activities that assist pharmaceutical companies in identifying and creating new markets. Lentacker (2016) found that the inclusion of generic drug names, which appeared on brands, patents and clinical trials, become a powerful marketing tool.

Sourcing strategy requires choosing the optimal sourcing combination to decrease the cost and increase the efficiency in clinical trials and new drug development processes. Due to the huge cost and high risk of clinical trials, organisations and academic researchers try to decrease these costs and risks through employing a sourcing strategy. Thakur-Wernz et al. (2020) analysed four types of sourcing strategies in clinical trials and found that the greater complexity of clinical trials leads firms to choose captive offshoring more often than domestic in-house sourcing. However, when clinical trial uncertainty increases, firms prefer to use domestic in-house sourcing over captive offshoring. Compared to other alternative sourcing choices, domestic outsourcing significantly decreases clinical trial costs and duration. Mehta & Peters (2007) found that firms prefer to transfer some clinical trials with less core technology and huge costs to contract research organisations to save resources and create high returns. The contract research organisations accumulate resources and knowledge via clinical trial outsourcing activities and, finally, grow into independent competitors.

Phase and approval success of new drug development refers to new drug candidates achieving success during the process of clinical trials, including phase success and approval success. The new drugs are required to pass all phases of clinical trials and receive approval from the government before they are launched on the market. The preconditions of commercialisation are the phase and approval success of new

drug development, which also attracts some attention from academic researchers. The literature review finds that the reasons for success in clinical trials are as follows: the ability to translate knowledge between basic and applied research (Haeussler & Assmus, 2021); combining the trust of different actors with methodological and institutional control in clinical trials (Bijker et al., 2016); understanding patients needs and good internal and external communications (Shaw, 1985); and maintaining absorptive capacity (Lowman et al., 2012). In addition, Chiou et al. (2016) found that patents associated with successful clinical trials receive more citations than those associated with failed clinical trials. Buonansegna et al. (2014) concluded with a list of factors that cause the failure of clinical trials, including the following: chaotic and slow patient recruitment; lack of experience in choosing and monitoring partners; lack of feasibility of the study protocol; low quality of the registered data; an overly high incidence of serious adverse events and severe incidents; an unmanageable level of portfolio complexity; and the incorrect assessment of the market potential or returns. Although the majority of new drug candidates fail in clinical trials, negative research findings are meaningful because the researcher can link these failures with their previous clinical trials and accumulate valuable experiences for future research (Timmermans, 2011).

Economic performance of the new product development includes the cost and income in new drug development. The main reason companies develop new drugs is to improve economic performance. Some articles proved that although some new candidates achieve good results in clinical trials, the companies have to give up them after considering the costs and future returns of these candidates (Fogel, 2018). Thus, predicting economic performance and detecting the factors on economic performance are also hot subtopics in the academic area. Favato et al. (2007) developed a method to estimate the cost of clinical trials to reduce the uncertainty of the cost estimates according to parametric analysis. Charalambous & Gittins (2008)

provided a C++ program to calculate the rewards and the optimal number of compound candidates in clinical trials. Bryde & Joby (2007) provided a new approach based on the concept of Product-Based Planning to manage clinical trials.

Quantitative studies have established some of the factors which influence the economic performance of new drugs and the cost of clinical trials, including the following: the basicness of the research; the size of the investment; the specificity of the scientific targets; the sustainability of the research direction after the cessation of funding; the probability of research and commercial success; the difficulties of actually introducing the therapy on to the market (Kenney & Patton, 2018); the safety and clinical efficacy testing; compliance with regulations; and the adequate protection of intellectual property (Curreli et al., 2008).

Innovation risk involves the unintended consequences in clinical trials and new drug development, e.g., failing to meet the quality of clinical trials and low returns of new drugs. The main characteristic of clinical trials is high risks; thus, the reviewed articles also concluded what were the innovation risks and the factors on innovation risks in clinical trials. Rocha et al. (2018) compared the different phases of clinical trials and found that the risk of phase 3 clinical trials is the highest. The high risks deter organisations from participating in innovation activities; thus, some articles focus on improving the confidence in innovation and incentives for innovation engagement. Johnson & Moultrie (2012) developed a technology confidence scale to assess the potential viability of new technology in clinical trials. Grönqvist & Lundin (2009) confirmed through vertical differentiation predictions that pharmaceutical companies obtain benefits from carrying out voluntary post-approval clinical trials by raising prices for both high-quality and low-quality drugs. Magazzini et al. (2016) found that there is a positive relationship between market size and firm entry in clinical trials. Higher-risk projects attract more firms to engage in clinical trials. The incentives are

different between large and small companies. Small firms prefer exploration with focus; however, exploration and exploitation are both beneficial to large companies (Mc Namara & Baden-Fuller, 2007). Gardner (2013) illustrated the importance of clinical assessment tools on innovation and commercial interests.

Innovation strategy is a plan made by an organisation to encourage advancements in clinical trials and new drug development, usually by investing in research and development activities. Innovation strategy is widely used in medical innovation to decrease the risks and increase the success rate of clinical trials. The reviewed articles investigate innovation strategy in the process of clinical trials. Bers et al. (2009) considered that the Accelerated Radical Innovation model helps solve the key issue in radical innovation, namely, the long, expensive and high-risk process of the clinical trial. Styhre et al. (2010) suggested four coping strategies in the case of clinical trials in a major multinational pharmaceutical company: understanding the organisational politics, demanding information and documentation, developing scenarios, and emotional work. Yaqub (2017) highlighted that a clinical trial is not only a regulatory requirement to verify the efficiency and safety of new technology but also an active process of learning and accumulating new knowledge. In addition, product choice and product development need to go hand-in-hand, because it is difficult to make a selection from amongst many long and costly innovation choices. Battard & Sébastien (2019) found that increasing openness and flexibility by including patients' experiences in clinical trials is good for innovation.

Introduction of new technologies in the medical area refers to using some new technology to cure diseases and improve efficiency in the medical area. The reviewed articles focused on the introduction of new treatments in the medical area, including the Internet of Medical Things (IoMT), blockchain, mobile

technologies and telemedicine. Doessel & Sams (1984) investigated fibre optic endoscopy and clinical trials of cimetidine and found the new treatment with cimetidine decreases gastric ulcer operations, but it does not reduce the number of patients in the case of duodenal ulcers. Hajiheydari et al. (2021) analysed the reasons for and against the use of the IoMT in clinics to improve managerial policies for introducing and successfully implementing IoMT technologies in hospitals. Jung & Pfister (2020) presented a framework concept for a blockchain-based distributed ledger solution for simple and secure management of written informed consent documentation, such as clinical study consent. Al Dahdah (2019) focused on mHealth, a health project assisted by mobile technologies, and found that the core of this programme gradually diverges in the journey from clinical trials to the market. Escobar et al. (2021) illustrated that telemedicine increases the speed and efficiency in clinics, simplifies the self-management of patients and allows patients to be more autonomous. However, there are only a few organisations using telemedicine, because doctors are not well enough trained to be able to adopt it.

Innovation clusters are groups of interconnected companies and associated institutions in clinical trials and new drug development processes, including network clusters and geographic clusters. Clinical trials and new drug development are always developed with the cooperation of members. The innovation clusters are generated through the cooperation of members in clinical trials and also attract some attention from academic researchers. Oudshoorn (1993) found that clinical trials bridge the relationships between the pharmaceutical industry, the laboratory and the clinic, resulting in a network of actors collectively creating medical knowledge, drugs and markets for these drugs. Rake et al. (2021) declared that the cooperation network is fragmented in clinical trials, which hinders knowledge transfer between actors. In terms of geographic clusters, Auerswald & Dani (2017) found that the cluster in the National Capital Region's entrepreneurial

ecosystem is in the conservation phase of its life cycle, according to the increasing number of large biotech firms, increasing diversity of start-up sectors, increasing merger and acquisition activity and decreasing public funding for clinical trials.

2.3.2 Scientific knowledge production

Scientific knowledge production refers to the generation of medical publications, patents and clinical trials, involving aspects such as research quantity, research quality and geographical distribution of research organisations. Understanding the process of scientific knowledge production and productivity of scientific knowledge helps to find valuable potential drugs and predict the results of clinical trials' conducted with them. A number of reviewed articles focused on scientific knowledge production. The literature review of this topic deals with scientific knowledge production patterns and the relationship between scientific impact and clinical trials.

Patterns of scientific knowledge production refer to using some analysis methods, including bibliometric analysis, regressions and descriptive statistics of publications, patents and clinical data to describe scientific knowledge production. Describing the patterns of scientific knowledge production helps to compare the research gaps in medical areas and find effective ways to improve the production of scientific knowledge.

Some reviewed articles focused on scientific knowledge production in different countries. Brives (2013) used a routine visit in a clinical trial conducted in Burkina Faso and found that scientific research should include patients and their families in clinical trials. Cartes-Velásquez & Manterola Delgado (2014) analysed dental publications by bibliometric evaluations and found that the research productivity increased in some

countries, such as Brazil, China, India and Turkey. The research productivity of the Nordic countries was at a high level; however, the USA was at the top of research productivity worldwide. Alam El-Din et al. (2016) used the bibliometric method to analyse the research productivity of the Hepatitis C virus (HCV) in Egypt and found that few controlled clinical trials were published on HCV in Egypt. Saquib et al. (2018) suggested that future scientific research should focus on running clinical trials on type 2 diabetes mellitus (T2DM) in Saudi Arabia.

The reviewed articles also analysed the scientific knowledge production of some specific diseases. Ávila-Robinson et al. (2019) analysed the publications, patents and clinical trials of induced pluripotent stem (iPS) cells for the treatment of degenerative eye diseases and found there are four factors influencing the evolution of new cell therapies, including the diversity of technological possibilities, the role of subjective issues in the selection of research directions, the complementary nature between established and emerging therapies, and tight product-process interdependencies. Hsiehchen et al. (2017) characterised the dynamic growth of biomedical research and clinical trials. They found that funding programmes permitting greater investigator autonomy enhance the sensitivity of research efforts to evolving health needs. In addition, research efforts into specific diseases are very well predicted by past NIH funding priorities. There are two articles about COVID-19. Pal (2021) analysed the publications on COVID-19 to summarise the scholarly output in this area, revealing that the clinical trial is an associated term in this area. Hanisch & Rake (2021) focused on repurposing in clinical trials of COVID-19 and found drug repurposing to be a predominant innovation strategy, but one which also caused insufficient variety and novelty in clinical trials.

There are also some articles focusing on the production of medical journals and publications. Ojasoo et al. (2001) found that the advent of randomised controlled trials and the accumulation of a critical mass of

literature increased the rate of publication of research syntheses, such as meta-analyses and practice guidelines. Wang et al. (2020) reviewed the publications in top medical journals, including Cell, JAMA, The Lancet and The New England Journal of Medicine (NEJM) in the year 2010 and examined the F1000Prime rating scores of these publications. F1000 Faculty members recommended clinical trial-related publications. Ngayua et al. (2021) found that the number of clinical trial-related publications in the areas of applied artificial intelligence, machine learning, deep learning and the internet of things has been increasing since 2010, and empirical approaches are progressively embraced in these articles.

Relationship between scientific impact and production of clinical trials. Due to the high risks, long periods and huge costs of clinical trials, developing valuable clinical trials becomes necessary. Scientific impact is increasingly used to predict the results of clinical trials. This literature review finds scientific impact is always calculated by citation frequencies and journal impact factors. The reviewed articles showed that the relationship between the results of clinical trials and the scientific impact of publications is complex. Akcan et al. (2013) found no correlations between the methodological quality of clinical trials and bibliometric indicators in the SBU systematic review of antibiotic prophylaxis in surgery. Romero et al. (2009) and Thelwall & Kousha (2016) found the papers which are cited by clinical trials have more citations than the other papers. Peritz (1994) made a meta-analysis of clinical trials and publications to find the determinants of citations received by those publications. The results show that citing authors prefer large studies to smaller ones and the inclusion of a placebo in the study design does not affect the related publications' citation counts.

Other researchers focus on the effects of publications, clinical trials, policies and collaboration on scientific impact. Kostoff (2007) compared the differences between highly and poorly cited publications in

the journal The Lancet. It found that the high citations are related to many authors, references, pages and the large sample sizes of clinical trials, along with specialist topics, including breast cancer, diabetes, coronary circulation and human immunodeficiency virus (HIV) immune system problems. Aleixandre-Benavent et al. (2019) suggested that the medical public data should be stored in PubMed Central and repositories of clinical trials. Chapa et al. (2017) analysed 242 randomised clinical trials to explore the determinants of scientific impact and social impact in Hepatitis C treatment. Ippoliti et al. (2021) found that collaborative networks in clinical trials foster the scientific impact of their members.

2.3.3 Knowledge transfer

Knowledge transfer is the movement of know-how, technical knowledge, or technology from one organisational setting to another in the process of new drug development (Roessner, 2000). Normally, knowledge transfer may occur between universities, hospitals, research institutions, businesses and governments, occurring across geopolitical borders, both formally and informally, and both openly and secretly. Whenever participants share skills, knowledge, technologies, manufacturing methods, samples and facilities, it is through knowledge transfer. Knowledge transfer bridges the gaps between scientific knowledge and new drugs or treatments; thus, knowledge transfer attracts some academic attention.

Robinson et al. (1985) highlighted the importance of bridging the knowledge gap between gene researchers and general practitioners to improve knowledge transfer from the molecular level to clinical trials. Grossman et al. (2001) found that the academic medical centre provides a distinctive environment for knowledge transfer by testing and improving medical devices and conducting essential clinical trials. Bourret et al. (2006) built the collaborative network of the *Groupe Génétique et Cancer* to detect knowledge transfer in multicentre clinical trials. Leonelli (2012) identified four key problems of integrating non-human data in

pre-clinical tests and human data in clinical trials to improve knowledge transfer between biologists and clinicians. Wadmann (2014) found that understanding the economic and moral valuations is necessary to improve knowledge transfer in a public-private research environment through interviews with clinician researchers and industry executives. Zvonareva (2021) argued that clinical trials exclusively focus on establishing a similarity between the trial and the clinic for greater generalisability and ignore consistency between medical experimentation and the conditions, needs and concerns in the clinic.

2.3.4 Institutional frameworks

The institutional frameworks regarding clinical trials are a set of policy measures and regulations to design, conduct and evaluate clinical trials to improve health outcomes and health service delivery following ethical requirements. The aims of the institutional frameworks are the following: 1) to safeguard participants in clinical trials; 2) to support clinical research that benefits individuals of all sexes/genders, races, ethnicities and ages; 3) to enhance the ethical and scientific quality of research; 4) to mitigate risk and avoid research waste. With the development of medical technology, the conflicts and debates between ethics and clinical trials become serious, which leads academic researchers to develop institutional frameworks to solve these conflicts and debates. The reviewed articles include healthcare policy, standardisation of clinical trials, bioethics, research bias in clinical trials and the epistemic practices of medical research.

Healthcare policy refers to the decisions, goals and actions that determine how care is administered and accessed. The healthcare policy is the basic guideline for developing clinical trials, taking care of patients and solving public health issues. The reviewed articles pay attention to the different healthcare policies in different counties and the impact of healthcare policy. Malik (2019) analysed clinical trials from China and India and found that the pre-and post-morbidity interventions vary between countries and for different

diseases. The analysis also suggests that in national policies, preventive measures are better than curative measures.

In addition, neoliberal pharmaceutical science has an impact on healthcare policy. Neoliberal scholars at the Chicago School of Economics generated both arguments and methods for controlling regulatory bodies in clinical trials (Nik-Khah, 2014a). They also constructed highly influential drug development institutions to influence clinical trials, pharmaceutical policy and science (Nik-Khah, 2014b).

Standardisation of clinical trials. The process of the clinical trial follows a range of standards to ensure the efficiency and safety of new drugs and enable the research results to be comparable. The standardisation of clinical trials is necessary to guarantee the performance of new drugs and new treatments. The reviewed articles focused on the standardisation contents, benefits of standardisation and barriers to standardisation. Richards (1988 & 1996) concluded that scientific evaluation of clinical trials cannot be achieved by methodological reform. Christensen et al. (2007) argued that the practicality of randomised clinical trials is inversely proportional to the complexity of the healthcare intervention. Abraham & Davis (2009) developed the concept of the "permissive principle" to ascertain the departure between practices and standards of drug evaluation in clinical trials. Even though both the UK and the USA have adopted the permissive principle and permissive regulation of specific drugs, this should not be regarded as an inevitable result of marketing strategies. Merz (2020) advanced recent interventions to avoid the problems of the non-standardisation of clinical trials.

The benefits of standardisation of clinical trials are reshaping three core processes of medical practice, including modification of material environments, the reorganisation of bureaucratic relations and the prioritisation of research values, by altering the organisations in which both medical treatment and clinical

trials take place (Petty & Heimer, 2011).

Although the standardisation of clinical trials provides some positive effects, Montgomery (2017) argued that some standardisation may be antithetical to sustainable and relevant clinical research and discussed the negative effects of standardisation in the following three dimensions, including the external validity of evidence from pragmatic trials, the gap between experimentation and implementation, and long-term site capacity to conduct research. Rosemann & Chaisinthop (2016) observed that, due to the absence of internationally harmonised regulatory frameworks in clinical trials and the presence of lucrative business opportunities, there is a trend toward the pluralisation of the standards, practices and concepts instead of standardisation in the clinical stem cell fields.

Bioethics focuses on the ethical issues emerging from advances in biology, medicine and technologies. Observance of acceptable ethical behaviour is compulsory for good clinical research; however, with developments in medical research, the principles and values of ethics are debated. Therefore, some academic researchers pay attention to balancing the conflicts between the efficiency of clinical trials and bioethics. The following factors increase the risks of unethical behaviour in clinical trials and drug development, including regulatory reforms, insufficient empowerment of regulatory agencies and disconnection between agents (Rodríguez, 2010), a perceived homogeneity of studies, Fordist work regimes and data-centric discourse (Fisher, 2014), increasing reliance on clinical trials in contemporary health care (Will, 2009) and financial interests (Adams, 2002; Hedgecoe, 2014).

Some researchers try to decrease the risks of unethical behaviour in clinical trials. Jasanoff (2002) questioned whether the courts can legitimately take on board the issues of risk and social justice in clinical trials. Epstein (2008) highlighted eliminating health disparities by race in participant enrolment in clinical

trials. Simpson & Sariola (2012) argued localisation resolves conflicts between the standards of clinical trials and existing epistemic virtues. Rayzberg (2019) found that geographic separation, temporal delay and public randomisation ceremonies to be the functions which solve the ethics of resource allocation in clinical trials. Löwy (2016) highlighted that it is necessary not only to focus on the criminal activities of doctors but also to prevent the numerous ethical transgressions of "normal" medical science and routine clinical practice. Brenman & Milne (2021) criticised the threshold for "clinical trial readiness" caused by an opaque and highly speculative drug development pipeline.

There is also a debate on special diseases related to ethics in clinical practice, such as human embryonic stem cells (HESCs) and human immunodeficiency virus (HIV). HESCs are the subject of research that requires destroying the embryo; thus, there is a conflict between ethics and technology development. Brunet (2017) focused on the establishment of a normative ethical barrier against clinical research on HESCs. Marks (2011) argued that reflexivity increases the trust between science and public trust. It is important to solve the HESC-related ethical issues in clinical trials. Sleeboom-Faulkner (2016) explored the diverse reasons and aims of patients, medical professionals and life scientists to develop HESCs and illustrated that ethical standards are not suitable for distinguishing between adequate and inadequate treatments in HESCs.

HIV is a good case for the discussion of bioethics. The difference and inequality in global health research increase the ethical problems around HIV in clinical trials (Crane, 2010). Davis (2020) argued that, in failing to grapple with the social realities that underlie poor adherence, HIV pre-exposure prophylaxis clinical trials produce knowledge that is not useful for vulnerable patients. The clinical trials, medical practices and products of vaginal microbicides for HIV prevention are used to analyse the ethical issues of sexism and feminism (Montgomery, 2012; Van Der Zaag, 2017).

Research bias in clinical trials is described as systematic errors that encourage one outcome over others in clinical trials. Bias distorts the truth and diminishes the reliability of clinical trials and may significantly mislead future research. Therefore, academic researchers analysed research bias in clinical trials to detect its effects. Krimsky (2013) argued that the funding effect is not definitive evidence of bias, but is prima facie evidence that bias may exist. Systemic bias exists in industry-funded clinical trials, but it does not appear in clinical trials funded by non-profit organisations. Salandra (2018) found that the percentage of selective reporting is higher for industry-funded clinical trials than for publicly funded clinical trials. In addition, compared with incremental innovation, radical innovation is more likely to opt for selective reporting. Schneider et al. (2020) found that biased knowledge is spread by falsifying data, 11 years after the fraudulent clinical trial report was retracted.

Epistemic practices of medical research are the activities associated with knowledge production and use in the medical area. The reviewed articles focused on how to increase public medical epistemic. Struhkamp et al. (2009) analysed the doctors and patients in rehabilitation laboratories and clinical trials and found that knowledge is aggregated through the interactions between doctors and patients in long-term treatment and daily life. Epstein (1995 & 1997) analysed the case of HIV clinical trials and found that lay activists are helpful in raising awareness of drugs by creating credibility between researchers and government.

2.3.5 Data gathering computer tools

Data gathering computer tools are computer programs used to collect and clean data. These tools are applied to deal with clinical trials data and draw conclusions based on the trials. The review of this literature found four tools to deal with clinical trials data: Dimensions (Bornmann, 2018; Herzog & Lunn, 2018),

PublicationHarvester (Azoulay et al., 2006), Sci2 (Lightet al., 2014) and Trialstracker (Decullier et al., 2021).

Dimensions is digital science software that bridges formerly siloed content types including grants, publications, citations, clinical trials and patents together (Bornmann, 2018). In Dimensions, each publication is assigned to at least one field according to machine learning. However, Bornmann (2018) tested the reliability and validity of Dimensions through a small dataset based on specific fields, and Herzog & Lunn (2018) improved the training set to increase the reliability and validity of fields.

PublicationHarvester is open-source software for collecting clinical trials, regular journal articles, reviews and letters/editorials on individual life scientists (Azoulay et al., 2006). It interfaces with MEDLINE to search for researchers fast. However, it cannot provide publication and keyword data for researchers outside of the life sciences. Since MEDLINE does not display affiliation information, PublicationHarvester is useless in organisational-level research.

Sci2 is an open-source tool to support temporal, geospatial, topical and network studies according to paper, patent, grant and clinical trial records (Lightet al., 2014). Sci2 is able to deal with big data rapidly. It has added web services to run selected workflows online.

Trialstracker ranks sponsors according to the proportion of unpublished clinical trials by extracting data from clinicaltrials.gov. However, Decullier et al. (2021) found that Trialstracker greatly underestimated the number of publications. Thus, the NCT number is still a reliable means of collecting clinical trials and related publications.

2.4 Discussion

Taking into account the above revision of clinical trial-related Innovation Studies, this section offers

suggestions for future research. Sections 2.4.1, 2.4.2 and 2.4.3 provide suggestions for theoretical research, empirical research and data gathering, respectively.

2.4.1 Potential suggestions for theoretical research

The reviewed articles on clinical trial-related Innovation Studies mainly analyse some innovation phenomena empirically. Less than one fifth of the reviewed articles specify the theoretical framework[2] (19.4%, see Table 2.3). A few examine moderating (1%) and/or mediating (0%) relationships between variables, which indicates a certain lack of theoretical sophistication in clinical trial-related Innovation Studies. Sections 2.4.1.1 and 2.4.1.2 review two promising theoretical frameworks that may be useful for advancing the research on clinical trial-related Innovation Studies: the life cycle theory of drug development and the user innovation theory of clinical trials.

[2] The reviewed articles with theoretical frameworks were identified by searching for the terms “framework” and “theor*” in the full texts, in addition to a manual check.

Table 2.3 Target articles with theoretical frameworks (N=20)

Article	Theoretical framework
Ávila-Robinson et al. (2019)	Co-evolutionary and system-oriented perspectives framework.
Bers et al. (2009)	Life cycle framework.
Buonansegna et al. (2014)	A conceptual framework with seven critical management issues for explaining NPD failures in the pharmaceutical industry.
Epstein (2008)	Actor network theory.
Fisher (2015)	Institutional banalisation of risk theoretical frameworks.
Fishman (2004)	Technology studies framework.
Grönqvist & Lundin (2009)	Theoretical model with symmetric quality uncertainty.
Haeussler & Assmus (2021)	Framework of horizontal skills and vertical experience.
Hajiheydari et al. (2021)	An integrative theoretical framework to understand and explain clinical users' scepticism and resistance toward IoMT.
Lentacker (2016)	Economy of symbolic goods theory.
Magazzini et al. (2016)	Real options theory.
Malik (2019)	Social–nature–technology nexus framework.
Mc Namara & Baden-Fuller (2007)	Exploration–exploitation theory.
Rayzberg (2019)	Entanglement, disentanglement, and overflowing framework.
Richards (1996)	A "sociology of monsters" framework.
Rodríguez (2010)	Internationally acceptable minimum ethical requirements framework of clinical research.
Sleeboom-Faulkner (2016)	In/externalisation theory.
Styhre et al. (2010)	Garbage-can decision-making theory framework.
Thakur-Wernz et al. (2020)	Transaction cost economics theory, organisational learning theory and comprehensive sourcing decision framework.
Van Der Zaag (2017)	Actor network theory.
Yaqub (2017)	Analysis framework of testability, trajectories and infrastructure.

2.4.1.1 Life cycle theory of drug development

The product life-cycle theory refers to the process of a new product, from its entering to its leaving the market (Vernon, 1966). The product life-cycle theory has been extended to Innovation Studies, such as using

life-cycle theory to assess the innovation capability of a region or cluster (Auerswald & Dani, 2017). In this review, the product life-cycle theory is extended to drug development to analyse the innovation vibrancy and trajectory of drug development and to help advance research on clinical trial-related Innovation Studies.

According to the product life-cycle theory, the life cycle of drug development starts with new ideas for new drugs and ends with mature commercial drugs (Myers & Howe, 1997). There are four stages in the life cycle of drug development, including drug discovery, preclinical development, clinical research and commoditisation (Willmann et al., 2008). Researchers discover new drugs through new insights into diseases, multiple tests of molecular compounds and biological products, new treatments of existing drugs and new technologies. Thousands of drug candidates are tested in the discovery stage, but only a few of them pass the test and enter the next stage. In preclinical development, the toxicity of drug candidates is tested in vitro at the laboratory and in vivo in animals. Clinical research refers to testing the efficiency and safety of drug candidates on human beings with three phases of clinical trials. Clinical research always involves a great deal of time and cost, and most drug candidates fail due to bad results and high costs. Pharmaceutical companies launch new drugs on the markets and obtain returns in commoditisation. The safety of new drugs is still monitored by the FDA, and Phase IV clinical trials are carried out after the new drugs have been launched on the market.

Even though the life cycle theory of drug development was originally applied most often to ensure the safety of drugs (Urushihara & Kawakami, 2010) and monitor the process of drug development (Destro & Barolo. 2022), it has become increasingly applied as a theoretical framework for analysing the costs, rewards, risks and challenges of drug development (Baras et al., 2012; Nass et al., Khullar et al., 2020). Following this stream of literature, the life cycle theory of drug development appears to be a promising framework to

investigate clinical trial-related innovation research questions. For example, should scientific researchers who focus on drug discovery or preclinical development participate in clinical research? Should researchers find cooperators for clinical research according to their experience in drug discovery or preclinical development? Why is the innovation productivity of organisations low (or high) in different stages of drug development?

2.4.1.2 User innovation theory of clinical trials

User innovation refers to the innovation which is developed by users rather than producers (von Hippel, 1986). Some of the reviewed articles have found that users (patients) play an important role in clinical trials (Brives, 2013; Struhkamp et al., 2009). However, the reviewed articles have not applied the user innovation theory to analyse patient innovation in clinical trials. Thus, in this study, user innovation theory is extended to clinical trials, providing a paradigm to analyse who the users in clinical trials are and why users participate in clinical trials, according to the user innovation theory of drug development.

According to Bogers et al. (2010), the users in clinical trials include intermediate users (such as doctors and nurses) and consumers (such as patients and their families). Doctors develop the plans of clinical trials for patients with the testing of drugs, and nurses help doctors to implement clinical trials with patients. Doctors and nurses monitor and record the patients' reactions to the drug tests. Patients take the drugs being tested under the plans of clinical trials and report their experiences to doctors and nurses. The families of patients are also important in clinical trials, especially when the patients are children, elderly or disabled. For example, in clinical trials with children, parents evaluate the plan's clinical trials and make decisions on whether or not their children should participate in them.

Based on the user innovation theory, there are two reasons for users participating in clinical trials, namely, the clinical trial-related costs and benefits to users. The drug development-related costs (benefits) to users not only include the financial cost (benefit), but the costs (benefits) of knowledge and efficiency and safety of the tested drugs. It must be highlighted that the costs and benefits are different between intermediate users and consumers. Thus, it is necessary to identify users when analysing the motivation for user innovation. The user innovation theory of clinical trials provides a paradigm to analyse some clinical trial-related innovation research questions. For example, which motivations drive different users to participate in clinical trials? How can user innovation in clinical trials be capitalised on? How can the medical industry promote innovation of clinical trails through doctors, nurses, patients and patients' families?

2.4.2 Potential suggestions for empirical research

Taking into account the articles covered in this review of the most recent clinical trial-related Innovation Studies, the distribution of target articles according to methodology is now described, and some suggestions for potential empirical advances to this literature are offered.

Table 2.4 describes the distribution of target articles by methodology. Most of the articles in this review use qualitative analysis (53%), a few less use quantitative analysis (42%), and only a small number (5%) use mixed-method analysis.

Table 2.4 Distribution of articles by methodology

Methodology	Number of articles	Percentage of articles
Qualitative analysis	55	53%
Quantitative analysis	43	42%
Mixed-method analysis	5	5%
Total	103	100%

The findings of these articles have provided many insights, which have in turn led to the current opportunity to employ a broader range of methodological and empirical techniques to build an even richer and more contextualised understanding of clinical trial-related Innovation Studies with clinical trials. To this end, a brief review is provided on how specific quantitative and qualitative advances could be made to build this area of research and move it forward. Table 2.5 breaks down Table 2.4 by topic area. A detailed analysis is then conducted in the subsections below.

Table 2.5 Distribution of research topics by methodology (n=103)

	Qualitative analysis	Quantitative analysis	Mixed-method analysis	Total
Commercialisation	**19%**	**14%**	3%	**36%**
Scientific knowledge production	1%	**17%**	0%	**18%**
Knowledge transfer	5%	1%	0%	6%
Institutional frameworks	**26%**	8%	2%	**35%**
Data gathering computer tools	2%	3%	0%	5%
Total	**53%**	**42%**	5%	**100%**

Note. In bold: main categories (above 14%).

2.4.2.1 Potential suggestions for quantitative research

Many articles in this review employed purely quantitative methods (42%), especially on the topics of scientific knowledge production (17%) and commercialisation (14%). Most reviewed articles describe scientific knowledge production; however, only ten articles analyse causal relationships (see Table 2.6). Therefore, the study begins by considering some potential advances that could be made to research adopting such an approach: (i) the urge for more quantitative research about knowledge transfer and institutional frameworks in clinical trial-related Innovation Studies; (ii) the opportunity to analyse cooperation networks with clinical trials data; (iii) the possibility for causal regression analysis with clinical trials data; (iv) the potential for capturing a broader range of variables with clinical trials data; (v) the need to examine moderating and mediating effects with clinical trial data in Innovation Studies; and (vi) the reasons why more longitudinal research is needed with clinical trials data.

Table 2.6 Distribution of quantitative and mixed-method studies by quantitative methodology

Methodology	Number of articles	Percentage of articles
Descriptive analysis	32	67%
Correlational analysis	6	13%
Regression analysis	10	21%
Total	48	100%

First, quantitative research uses objective data to test the theory and understanding of the real world through statistics and numbers. There are fewer quantitative studies on the topics of knowledge transfer and institutional frameworks. One possible reason is that objective data is not available on these topics. For example, it is difficult to describe bioethics by data and there is no standardised dataset with patents, clinical

trials, publications and firm performance to analyse knowledge transfer. It would be beneficial to use more professional tools to build quantitative research in knowledge transfer and institutional framework, e.g., using machine learning to improve the efficiency of matching clinical trials data with other data or exploiting programming languages such as Python to deal with the clinical trials data.

Second, some of the reviewed articles have shown approaches to build cooperation networks with clinical trials data (Rake et al., 2021) and have analysed cooperation network structures in cooperation networks. Based on the approaches to build cooperation networks with clinical trials data and the existing theory of cooperation networks (Marques & Franco, 2020), more research questions could be investigated in the future, such as how knowledge flows in cooperation networks and what the impact of knowledge is on the performance of other members in the networks.

Third, most quantitative studies use descriptive or correlational analysis, and only a few include regression, so there is a need to develop studies with causal regression analysis. Future research could develop more regression analyses, such as the effect of scientific research on engagement on clinical trials and detecting whether patent protection promotes or hinders drug development.

Fourth, only ten articles calculate dependent and/or independent variables with clinical trial data (see Table 2.7). Most of the indicators evaluate whether a discrete event has occurred, e.g., success (Haeussler & Assmus, 2021), repurposed drug (Hanisch & Rake, 2021), selective reporting (Salandra, 2018) and clinical trials phase (Ippoliti et al., 2021). Future research could use finer-grained measures of the recurrence of the given event, e.g., the number of successful clinical trials or drugs, or the percentage of different clinical trials phase for a given firm. The reason for this situation is that the unit of observation is only in the clinical trial. However, the same factors that increase the probability of success of a clinical trial may not increase the

probability of success of another clinical trial. This may bias the results and give rise to misleading policy implications. For making full use of clinical trial data to build indicators, there is a need for more research levels, e.g., drugs and firms, to develop well-used policy implications. It would be advantageous for future research to consider how firms achieve success in drug development and to build variables at the firm level, e.g., the number of successful drugs for a given firm and the percentages of success in different clinical trials phase for a given firm.

Table 2.7 Dependent and independent variables based on clinical trial data in the regression-based target articles (n=10)

Article	Dependent variables	Independent variables
Haeussler & Assmus (2021)	*Success*: whether the drug, treatment or intervention is advanced to the next phase of testing in the same indication or is not advanced.	Diversity of experience.
Hanisch & Rake (2021)	*Repurposed drug*: binary variable equalling one if a drug is repurposed, that is, the drug has been applied to treat a disease other than COVID-19 before and zero otherwise.	Academic institutions, Biopharmaceutical firms, Device manufacturers, Hospitals, Governments, Days since first COVID-19 trial, Number of trial sites, International trial, Phase controls.
Magazzini et al. (2016)	*Cost of failures*: the average time spent in clinical trials by unsuccessful R&D projects. Success probability.	Specificity of R&D, Time before discontinuation, Standard deviation of time before discontinuation.
Mc Namara & Baden-Fuller (2007)		Six stages of the R&D process.
Salandra (2018)	Selective reporting.	Source of institutional support, Type of innovation.
Thakur-Wernz et al. (2020)	*Project cost and duration*: project level performance is measured by (i) the total cost of conducting the study and (ii) duration of the trial.	Inside organisational boundaries, Project complexity, Project uncertainty.
Rake et al. (2021)	*New connections to knowledge translators*: whether an investigator in the clinical trial network has established a new collaborative tie to a knowledge translator.	Preferential attachment, multi-connectivity.
Ippoliti et al. (2021)	*Citations per trial:* the number of articles citing specific phase II and III clinical trials.	R&D strategy of type 1(2/3/4), Phase II trials, Phase III trials, NME classified as first in class, Number of enrolled patient.
Malik (2019)		The number of participants—patients and volunteers, the number of sponsors of the clinical trial, the number of financiers.
Chiou et al. (2016)		The type of organisations.

Note. The variables in Marlik (2019) and Chiou et al. (2016) are control variables.

Fifth, Table 2.8 shows there is only one reviewed study with moderating factors, and that none of the reviewed articles consider mediating factors. The moderating factors avoid biased estimates resulting from omitted variable interactions and make the conclusions more reliable (Cohen et al., 2003). The mediating factors illustrate the reason for a causal effect in order to fully understand the effect mechanism (Cohen et al., 2003). For this field of research to mature, these complex causal relationships should be taken into consideration in future research, e.g., how to exploit scientific knowledge to develop clinical trials and increase the success rate of firms.

Table 2.8 Descriptive characteristics of target articles with regression analysis (n=10)

Study characteristic	Number of articles	Percentage of articles
Included moderator	1	10%
Included mediator	0	0%
Did not include moderator or mediator	9	90%
Cross-section data	7	70%
Panel data	3	30%

Sixth, due to a reliance on the use of cross-sectional data (70%), research examining the commercialisation process from clinical trials to product, knowledge transfer from scientific research to applied research and the policy effect of clinical trials has been incorporating the variable of time and adopting a process perspective. This situation presents a critical problem due to the lack of longitudinal studies that account for whether an event has led to a value-adding outcome, meaning it is hard to develop well-informed policy implications. For example, some factors that increase engagement in clinical trial activities could simultaneously undermine the success rate of clinical trials. Thus, to develop well-informed policies, there is a need for more longitudinal research that considers the unfolding process of engagement

in clinical trials along with the actual outcomes that are ultimately produced by such efforts.

2.4.2.2 Potential suggestions for qualitative research

The majority of qualitative studies in this review deal with the topics of institutional frameworks (26%) and commercialisation (19%). One reason for the high percentage of qualitative research on these two topics is that the approaches to clinical trial-related Innovation Studies are at the primary stage; thus, it is necessary to obtain clear theoretical ideas through qualitative research. The other reason is that it is difficult to conduct clinical trials data analysis for the studies on institutional frameworks and commercialisation. Qualitative analysis allows researchers to introduce novel theoretical ideas (Glaser & Strauss, 1967) and answer questions that are less capable of being managed through deductive quantitative approaches (Edmondson & McManus, 2007; Eisenhardt, 1989). For example, questions dealing with decreasing the risk of unethical behaviour in clinical trials require the observation of clinical trials practice in order to raise some suggestions.

Although there are many reviewed commercialisation articles with qualitative analysis, the field still needs to develop more research with other qualitative analysis methods, such as grounded theory. Grounded theory refers to conducting qualitative studies with a set of systematic inductive methods aimed towards theory development. The novel theoretical ideas in commercialisation articles could be introduced based on the observation of clinical trials and the returns from new drugs, resulting in rich insights into commercialisation processes and behavioural interactions. For example, questions regarding the strategy in conducting clinical trials of organisations with new drugs or with already tested drugs would seem to call for observations of the circumstances and intentions that inform such decisions. Much work remains to be done to fully understand a wide range of motivation-oriented questions, including understanding what aims organisations have when carrying out clinical trials during the commercialisation process.

Only a few reviewed articles on the topic of scientific knowledge production employed qualitative analysis (1%). One possible reason for this is that the reviewed articles mainly focus on the description of scientific knowledge production and display the relationship between the scientific impact of publications and the production of clinical trials. This lack of theoretical research on scientific knowledge production studies inspires some suggestions. Future research could provide some reasons as to why the scientific impact of publications leads (or does not lead) to the production of clinical trials. According to the reviewed articles, the relationship between the scientific impact of publications and the productivity of clinical trials is sometimes positive (Romero et al., 2009; Thelwall & Kousha, 2016) and sometimes not significant (Akcan et al., 2013). Thus, there is a need to generate some theories through qualitative research to explain the unstable relationship between the scientific impact of publications and the productivity of clinical trials.

Case studies provide new insights to develop institutional frameworks articles, since case studies allow researchers to develop a deep understanding of multi- and cross-level phenomena and provide theory to support later quantitative multilevel modelling strategies. Future institutional frameworks can extend the theory border through case studies. For example, the reviewed articles found research bias in clinical trials (Schneider et al., 2020) and some reasons for research bias, such as funding sources (Salandra, 2018). Investigations into the effect of methods to decrease research bias and the results of research bias in clinical trials are still very limited. Future research could take some special cases of research bias to explain why some methods are more effective than others in decreasing research bias and analyse the consequences of research bias in clinical trials.

Although some reviewed knowledge transfer articles use qualitative analysis, this method is still at the primary stage (only 5% of the reviewed articles use qualitative analysis on knowledge transfer). The

reviewed knowledge transfer articles mainly highlight the coordination of inter-organisational relationships to improve knowledge transfer, such as cooperating with academic medical centres (Grossman et al., 2001), building a cooperation network (Bourret et al., 2006) and coordinating the relationship between academic medical centres and clinics (Zvonareva, 2021). Further qualitative research can extend the theory border to consider the what effects public policy and the characteristics of scientific knowledge, such as the basicness of its scientific impact, have on knowledge transfer.

2.4.2.3 Potential suggestions for mixed-method research

Mixed-method analysis research combines quantitative analysis and qualitative analysis to answer the research question. It is helpful in explaining a complex situation in order to reach a general conclusion. However, only a few reviewed articles (5%) applied mixed-method analysis to investigate the clinical trials in innovation. One possible reason is the lack of effective methods for collecting related data and developing quantitative analysis to meet qualitative research. While the reviewed articles provide some methodologies to collect clinical trial data, there is a need to develop more mixed-method analysis studies, such as discussing sexism related to the genders of participants in clinical trials and comparing the effectiveness of healthcare policy through the performance of clinical trials in different countries.

2.4.3 Potential suggestions for data gathering computer tools

The reviewed articles present four tools to gather clinical trials data. These tools help researchers to collect and deal with clinical trials data easily. However, these four tools are unable to meet the requirements of clinical trial-related Innovation Studies. First, Dimensions links clinical trials data with publications and patents data, but some researchers doubt its reliability and validity (Bornmann, 2018). Thus, future research

could develop more professional tools to improve the reliability and validity of data matching, such as using machine learning by Python to deal with clinical trials, publications and patents data. Second, there is a lack of studies to test and support the effectiveness of these tools. Therefore, future research could try to apply these tools and provide more evidence to support their effectiveness. Third, the existing articles provide some indicators of clinical trials, which could be added to these tools to demonstrate the production of clinical trials.

2.5 A brief overview of the literature on drug development outside Innovation Studies, with a focus on emerging trends in the analysis of clinical trials

Of course, the literature on clinical trials expands beyond Innovation Studies. Although it is beyond the scope of this paper to conduct a systematic review in other fields, knowledge of the broader available material was employed to make selected contributions, specifically from the medical and management fields. Three trends in the analysis of clinical trials are focused on, which present potentially important implications for clinical trial-related Innovation Studies: applying artificial intelligence in clinical trials, developing personalised drugs, and applying competitive strategies on patents.

Artificial intelligence (AI), as a promising technology to reduce costs and increase the success rate of drug development, is gradually being applied in clinical trials (Lou & Wu, 2021). The predictive computational function of AI has contributed to discovering candidate compounds and evaluating the safety and efficiency of these candidate compounds (Thomford et al., 2018). The natural language processing technology of AI increases the matching rates between patients and clinical trials and saves cost and time in clinical trials (Woo, 2019). The analytical and computational techniques of AI are also applied to analyse the

reports of clinical trials and monitor the feedback on new drugs on the market (Firouzi et al., 2021). Applying AI technology in clinical trials provides some new insights to develop clinical trial-related Innovation Studies. For example, what are the benefits and challenges of applying AI in clinical trials? How can the innovation productivity efficiency of clinical trials be increased through AI?

Advances in molecular pathology and immunology make personalised drugs possible. Personalised drugs refer to the tailoring of drug treatment to patients according to their DNA sequences. For example, crizotinib works well on non-small cell lung cancer patients with rearrangements of the anaplastic lymphoma kinase gene. Some clinical trials of personalised drugs are increasingly being carried out for cancer, psychiatric disorders and Alzheimer's (Shemesh et al., 2021; Lee, 2019; Pluvinage et al., 2019). Since personalised drugs cure diseases according to patients' DNA sequences, the clinical trials of personalised drugs are always more costly and time consuming than non-personalised drugs. This, therefore, raises a research question for clinical trial-related Innovation Studies: which type of researchers and organisations have the capability to develop personalised drugs?

Patents are widely used to protect the intellectual property of drugs. Medical companies apply a series of patent competition strategies for clinical trials, such as cooperation and acquisition. Cooperation in patenting is a common way to develop clinical trials for, and launch drugs in, novel emerging markets (Mermelstein & Stevens, 2021). Through cooperation in patenting between medical companies and firms, new drugs are able to rapidly access recently emerging markets. Acquisition is used to acquire patents and reduce competitors in the market (Lee et al., 2019). Some medical companies even stop competitors' clinical trials and deter potential competitors through acquisitions (Cunningham et al., 2021). Thus, these competitive strategies based on patents call for further analyses of patent-related organisational activities in

future clinical trial-related Innovation Studies.

2.6 Conclusions and limitations

Some academic researchers are paying increasing attention to clinical trials in Innovation Studies, which deepens understanding of the process of new drug development. To summarise the clinical trial-related Innovation Studies in prior research, 103 clinical trial-related Innovation Studies in innovation journals from 1984 to 2021 were systemically reviewed. First, the topics of previous research were categorised. Second, the distribution of articles and research topics by methodology were described and some suggestions provided for potential theoretical and methodological advances of future research. Third, a brief overview of the emerging trends in the analysis of clinical trials outside Innovation Studies was made. The literature review identifies theories and methodologies in clinical trial-related Innovation Studies and provides a solid background for future research. Some ideas to develop theoretical and empirical research were also provided for academic researchers wishing to undertake studies on medical innovation.

Through this systematic review, five research topics of target-reviewed articles were summarised, including commercialisation, scientific knowledge production, knowledge transfer, institutional frameworks, and data gathering computer tools. Only 20 articles specified a theoretical framework, a small number, which raises the need for further theoretical emphasis. The distribution of reviewed articles and research topics by methodology shows that most reviewed articles use qualitative analysis (53%), especially in relation to the topics of commercialisation (19%) and institutional frameworks (26%). Slightly fewer reviewed articles apply quantitative analysis (42%), especially in the areas of commercialisation (14%) and scientific knowledge production (17%). Mixed-method analysis is barely employed in the reviewed articles (5%).

Theoretical and empirical suggestions were developed for each topic. In addition, some potential research areas were revealed based on emerging trends in clinical trials through a brief overview of medical and management journals. Table 2.9 displays these suggestions according to the two research questions: how can we improve the analysis of certain core topics of Innovation Studies (e.g., commercialisation, scientific knowledge production and knowledge transfer) through the analysis of clinical trials as a stage in the process of drug development (RQ1)? How can we improve the use of clinical trial data in Innovation Studies (RQ2)?

The empirical chapters of this PhD thesis (Chapters 3 and 4) draw on some of the recommendations in Table 2.9. For example, in topic "Commercialisation" (RQ1), the analysis of more factors with a complex relationship on drug development is suggested. This idea is developed in Chapter 3 by investigating the effect of radicalness and cooperation network density on the success of drug development. Then, in the topic "Scientific knowledge production" (RQ1), the suggestion is made to analyse the relationship with scientific productivity. This is developed in Chapter 4 by exploring the effect of scientific knowledge on the success of drug development. In addition, in the topic "Scientific knowledge production" (RQ2), the suggestion is made to apply the network view to investigate scientific knowledge production. This is developed in Chapter 4 by analysing the direct and research cooperation network spillover effect of scientific knowledge on the success of drug development.

Table 2.9 Recommendations for future research on clinical trial-related Innovation Studies

Topic	Research questions and theoretical frameworks
Commercialisation	RQ1. Reviewed articles on commercialisation have detected limited antecedents of the success of drug development, including knowledge translation ability, communication ability, absorptive capacity and trust. Further research can analyse more factors with a complex relationship on commercialisation, such as analysing the effect of the quality of scientific research and patent protection on the success of clinical trials. Future research can use grounded theory to explore whether to conduct clinical trials with new drugs or with already tested drugs and what aims organisations have when carrying out clinical trials during the commercialisation process. RQ2. The reviewed articles on the success of drug development only used cross-section data in empirical research. There is a lack of longitudinal research to support these results. Further research can test whether these results are still supported for a long period. Emerging trends: analysing the benefits and challenges of applying AI in clinical trials and exploring organisations' capabilities to develop personalised drugs. Useful theories: life cycle theory of drug development, user innovation theory of drug development.
Scientific knowledge production	RQ1. The reviewed articles found that collaboration is the key factor to achieve scientific impact. Since there are different types of cooperators (including firms, universities, hospitals, research centres and so on), further research questions are raised: who is the best cooperator in order to increase scientific impact? And how to maintain the relationship with cooperators to achieve success in clinical trials? The reviewed articles explore the relationship between the scientific impact of publications and the production of clinical trials. However, there is a lack of studies to explain why the scientific impact of publications leads (or does not lead) to the production of clinical trials. Future research could try to examine the channels that link scientific impact of publications to the production of clinical trials. RQ2. Few of the reviewed articles investigate scientific knowledge production through a cooperation clinical trials network view (Ippoliti et al., 2021). Future research could analysis the dynamic cooperation network from phase I clinical trials to phase III clinical trials to investigate scientific knowledge production in difference phases of clinical trials. Emerging trends: analysing the scientific knowledge base of developing personalised drugs. Useful theories: life cycle theory of drug development, user innovation theory of drug development.
Knowledge transfer	RQ1. The qualitative studies on knowledge transfer found some determinants of knowledge transfer, such as academic medical centres and cooperation networks. Further qualitative research can extend the theory border by considering more determinants of knowledge, such as public policy and the characteristics of scientific knowledge. The life cycle theory of drug development can be applied to analyse the knowledge transfer between the stages of drug development in future research. RQ2. The cooperation network of clinical trials provides new views to detect knowledge transfer from scientific knowledge to new drugs or treatments. Thus, future research can explore how technology flows in a cooperation network of clinical trials. What is the effect of network factors on knowledge transfer? Emerging trends: what is the effect of patent-related organisational activities on

Topic	Research questions and theoretical frameworks
	knowledge transfer, especially international knowledge transfer, in clinical trials? Useful theories: life cycle theory of drug development, user innovation theory of drug development.
Institutional frameworks	RQ1. Few reviewed articles explore institutional frameworks with quantitative research. Future research can undertake more quantitative research to explore the research questions on institutional frameworks, such as whether the health policy functions well on clinical trials and what factors cause research bias in clinical trials. Future research can employ case studies to explain the reasons for different methods of decreasing research bias and analyse the results of research bias in clinical trials. RQ2. Longitudinal research is needed in further research to observe the effectiveness of health policy and standardisation of clinical trials over a long period. Emerging trends: analysing ethical issues on applying AI in clinical trials and developing personalised drugs. Useful theories: user innovation theory of drug development.
Data gathering computer tools	RQ1. There is a lack of studies to support the effectiveness of these tools. Further research can provide more evidence to apply these tools to build indicators which test their effectiveness. RQ2. The reviewed articles on computer tools displayed some tools to deal with clinical trial data. However, these tools are still limited. Therefore, it is desirable that more professional tools be developed, e.g., using machine learning to improve the efficiency of matching clinical trials data with other data; exploiting programming languages such as Python to deal with the clinical trials data.

This chapter provides potential theoretical and methodological suggestions for future research. First, by raising awareness of the importance of developing Innovation Studies related to clinical trials. Since clinical trials are special stages of new product (drug) development, which are near the market, analysing clinical trials deepens the understanding of the process of new product development. Second, the potential theoretical and methodological suggestions provide guidelines for developing future clinical trial-related Innovation Studies. Based on the systematic literature review, it can be concluded that the analysis of clinical trials has been underexplored in the field of Innovation Studies. It is suggested that the life cycle theory of drug development and user innovation theory of drug development be applied in future research. In addition, it is proposed that longitudinal datasets be developed to analyse more factors and complex causal

relationships in future research. Third, some new ideas are provided for exploring innovation studies of new product development, especially drug development, through analysing clinical trials. Drug development-related Innovation Studies have been well explored through patents, publications and firm performance. It is suggested that clinical trials are promising research objects to investigate innovation research questions of drug development, since they are necessary elements in the market stages of drug development.

There are still some limitations to this research. First, since the focus is on clinical trial-related Innovation Studies, target articles were sought in innovation journals to meet the research questions. Innovation articles on clinical trials in medical journals were not included. Although most of the clinical trials-innovation articles in medical journals address medical research questions instead of innovation research questions, they may provide some insights into developing clinical trial-related Innovation Studies. To a very limited extent, this issue was addressed in Section 2.5, but further attempts to conduct a systematic literature review would be recommendable.

Second, the literature review was undertaken based on clinical trials, the key stage of drug development, to understand innovation research questions in clinical trials. However, this choice may have caused other activities involved in drug development to be overlooked, such as patenting and animal tests. Future research can extend the literature review with further activities involved in drug development.

Chapter 3

Success of drug development for cancer diseases: radicalness and network density

3.1 Introduction

In the pharmaceutical industry, the efficiency of new drug developments has been declining for decades (Scannell et al., 2012). This has lead organisations to adopt various methods to increase the efficiency of new drug development in different sectors (Inauen & Schenker-Wicki, 2012; Robbins & O'Gorman, 2015; Consoli et al., 2015). The development of a new drug follows a standardised chain of events that begins with basic research and ends with the market launch of a new drug (Molas-Gallart et al., 2016). In general, it takes around eight years to develop a new cancer drug before commercialisation can begin (e.g., Kaitin, 2010; Kaitin & DiMasi, 2011; Puthumana et al., 2018). Since the 1990s, research on genetic alterations in human cancers has led to a better understanding of the molecular drivers of cancer diseases. This knowledge could theoretically provide more useful drugs in the field of cancer treatments, but the effectiveness of drug development is still remarkably low (Hutchinson & Kirk, 2011). Compared with other therapeutic areas, drug development has the highest failure rate in the field of cancer disease treatments (Begley & Ellis, 2012). For these reasons, it is necessary to increase the success rate of cancer drug development.

According to Hay et al. (2014), there are two types of success in drug development: "phase success" and "success of approval". "Phase success" means that the drug enters into one development phase of a clinical trial, achieves a good result, and begins the next phase.[3] "Success of approval" means that the drug is approved by a national authority (notably, the U.S. Food and Drug Administration — FDA). This research focuses principally on the final success of drug development: "Success of approval". Drug development is time-consuming, costly, risky and complicated, which hinders the productivity of the pharmaceutical

[3] Clinical trials are divided into different phases. The phases of clinical research are the steps in which scientists perform experiments in medical interventions in an attempt to gather enough evidence for a process to be proved useful as a treatment.

industry and the success rate of drug development (Hay et al., 2014). The high unmet need of patients and huge market size leads to many sub-optimal pre-clinical drugs entering in vivo testing in cancer diseases. The success rate of cancer drug development increases by raising standards of pre-clinical cancer research and accumulating more basic knowledge (Begley & Ellis, 2012). Building a diverse drug development co-operation network — including companies, hospitals, universities, public or private research centres and patient groups — is also a method for sharing risks, targeting different research beneficiaries and improving the approval success rate of drug development (Kaitin & DiMasi, 2011; Caner et al., 2017; Azagra-Caro & Llopis, 2018). The general objective of this research is to acquire a greater understanding of how to promote successful drug development in cancer diseases. More specifically, the role of two mechanisms will be investigated: the radicalness of drug development and the effect of research co-operation network density — the importance of which will be explained below.

Although cancer drugs continue to dominate the drug approval list in the therapeutic area (Mullard, 2018), the mortality rate of cancer diseases is still higher than for other non-communicable diseases (World Health Organisation, 2017). Most cancer patients without effective drug medication require radical developments to cure their disease. This "radicalness" refers to drug developments involving new molecular entities or new therapeutic biological products, which supplant existing drugs to cure a disease.[4] In the history of drug development, the success of radical drug development not only substantially reduces costs and improves efficiency but also decreases patients suffering, promotes the health of human beings and

[4] The definition used in this study is based on the classification of drugs by the FDA (2015), and the definition of radical innovation is according to the theory of Christensen (1997) in which radical innovation is a new paradigm that transforms or replaces existing products with high income. Other definitions of radical innovation focus on the contrast with incremental innovation. Radical innovation changes existing technologies or marketing structures, whereas incremental innovation uses existing technologies to improve processes or products for existing markets (Garcia & Calantone, 2002).

brings social value, whether it involves small molecules or biological products. However, in general, the success rate of radical drug development is less than 10% (Lo, 2017) with a cost of US$ 802 million per new drug (DiMasi et al., 2003). The first concrete objective of this study is to analyse the effect of radicalness on the success of drug development in cancer diseases.

Research co-operation networks provide pharmaceutical organisations with external knowledge and resources to develop drugs. A great deal of knowledge and resources are embedded in an interactive strategic alliance that benefits the actors and other members of the group (Portes, 1998). Network density is the density of connections between members in the network (Mitchell, 1969). It reflects an organisation's capability to search for, gather and acquire external knowledge and resources (Hansen, 1999; Phelps, 2010). Formulating appropriate innovation strategies according to the network density is beneficial to organisations achieving success. The second concrete objective is to investigate the role of network density in the success of drug development in cancer diseases.

Previous research has not addressed the relationship between radicalness, network density and success in the drug development stage. With these two specific objectives, this research aims to address this gap. A possible reason why this has not been attempted before may be the lack of a method to link indicators of radicalness and success. Other works have measured radicalness (Omta et al., 1994; Jong & Slavova, 2014; Coccia, 2017) or success (Hay et al., 2014) separately, but this study seeks to go a step further by proposing a method of overcoming the difficulties in their joint analysis.

3.2 Literature review and hypotheses

In this section, the relationship between radicalness, research co-operation network density and the

success of drug development is analysed. Figure 3.1 shows the research framework and hypotheses.

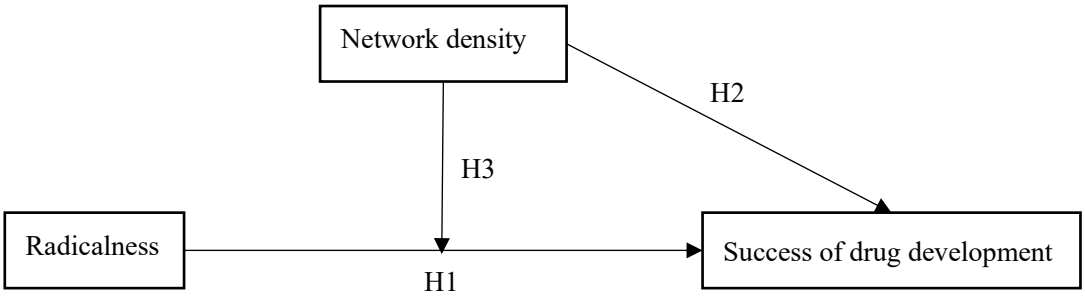


Figure 3.1 Research framework and hypotheses

3.2.1 Radicalness and success of drug development

According to González et al. (2017), innovation radicalness refers to "a novel solution which has distinctive features that are missing in previously observed solutions, and that has a very positive impact on society and/or the environment". Following this definition, an organisation with high radicalness is an organisation that develops a large amount of genuinely new drugs and that provides many new opportunities to cure cancer diseases, whereas an organisation with low radicalness focuses on enhancing or modifying existing drugs.

Organisations with high radicalness need to combine innovative knowledge and technology into these new drugs to improve their benefits and cure diseases, especially diseases without a specific medicine. Organisations with high radicalness always receive huge amounts of returns and long-term competitive advantages in the new drug development. However, organisations with high radicalness alsoface a great number of potential risks in the drug development process (Rajashekar & Abimanyu, 2020). First, due to

pessimistic predictions regarding the performance of new drugs and the huge investment involved, organisations may terminate promising new drug development in the early stages (Buonansegna et al., 2014). Second, high radicalness invariably relies on a substantial measure of innovative knowledge and resources (Sternitzke, 2010). Due to the limitations of knowledge and resources, organisations with high radicalness regularly take significant scientific risks in the drug development process (Rajashekar & Abimanyu, 2020). Third, the long periods involved in new drug development also pose economic risks for these organisations with high radicalness, as the likelihood of a competitor making the new drug first increases, leading the economic benefits of the new drug development to decrease. Organisations with high radicalness prefer to end new drug development processes which have less promising returns (Dickson & Gagnon, 2009). Thus, the organisations with high radicalness face high failure rate of drug development.

In contrast, organisations with low radicalness are less dependent on innovative knowledge. In fact, previous clinical expertise is much more beneficial for these organisations (e.g., Aiken et al., 1980). Organisations with low radicalness always use existing knowledge, resources and products to improve the existing drugs and expand their market niche. They operate under a safety framework which tends to avert the potential risks in drug development. Thus, low radicalness provides organisations with a greater likelihood of achieving successful drugs. For these reasons, the first hypothesis is formulated as follows:

Hypothesis 1. An organisation's radicalness in drug development decreases its likelihood of succeeding in drug development.

3.2.2 Research co-operation network density and success of drug development

Network density is the proportion of the potential relationships in a network that are actual relationships (Mitchell, 1969). It reflects the extent of interconnectedness of network members (Tichy & Fombrun, 1979). With a low network density, direct connections between network members are relatively sparse, and organisations can focus efforts on drug development instead of coordinating co-operative relationships. However, a sparse network hinders the transfer and exchange of knowledge and resources (Tur & Azagra-Caro, 2018). With a high network density, most network members are connected, and the members exchange knowledge and resources directly (Ahuja, 2000). Thus, the knowledge and resources diffuse rapidly in a dense network, which is beneficial to drug development. However, a dense network may be laden with redundant relationships (Burt, 2000). The redundant relationships decrease the heterogeneity of knowledge and organisations have to make a great deal of effort to coordinate these relationships, which decreases the efficiency of drug development. Thus, the following hypothesis is proposed:

Hypothesis 2. The relationship between an organisation's research co-operation network density and the success rate of its drug development follows an inverted U-shape.

3.2.3 Research co-operation network density and the relationship between radicalness and the success of drug development

Due to the limitations of knowledge and resources, it is important for organisations to ascertain and select the optimal portfolio for drug development (Macher & Boerner, 2013). Many factors influence the selection of drug development portfolio. Among these, the capability of acquiring external knowledge has

been recognised as an important factor in the selection of drug development (Xu et al., 2013). Building research co-operation networks is an effective way to acquire external knowledge (Rothaermel & Boeker, 2008).

Organisations with high radicalness need the integration of distant and diverse knowledge (e.g., Cassiman et al., 2005; Kaplan & Vakili, 2015). A dense research co-operation network with an abundance of diverse co-operators is a good channel for radical organisations to gather diverse types of knowledge from external alliances. In addition, there are a greater number of uncertain outcomes for organisations with high radicalness than for those with low radicalness, such as overdose, toxic reactions and side effects. The dense network is also helpful to solve these risks, because it is replete with external knowledge from industry, academia and regulating authorities. For this reason, the final hypothesis is posited as:

Hypothesis 3. An organisation's research co-operation network density plays a positive moderating role on the relationship between radicalness and success rate of an organisation's drug development.

3.3 Model, data and methodology

An assessment will be made of the following model:

$$Success\ of\ Drug\ Development_i = f(Radicalness_i, Density_i, Density_i^2, Radicalness_i * Density_i, Control\ variables_i, \varepsilon_i)$$

Where *i* represents an organisation.

3.3.1 Data sources

Variables were established that referred to the process of drug development through information on

clinical trials[5] and FDA approved drug products for cancer diseases. The U.S. Clinical Trials Registry was chosen due to its larger number of records vis-à-vis other administrations (331,536 up to 2019; compared with, for instance, 36,638 clinical trial records in the EU Registry; 29,688 in the Chinese Registry; and 44,051 in the Japanese Registry). Data was gathered from several sources:

- **NLM Drug Information Portal**, which provides a gateway to gather drug information from the U.S. National Library of Medicine and other key U.S. Government agencies. The reason for collecting data from the NLM Drug Information Portal instead of ClinicalTrials.gov directly is that the latter only permits clinical trials to be searched for by "Condition or disease", which ignores the clinical trials of cancer drugs used to treat other diseases (e.g., hepatitis, uveitis, scleroderma and so on) and leads to some radical drugs being missed, thereby underestimating the success rate of drug development. Furthermore, the drug names should be collected from "Interventions" on ClinicalTrials.gov, but the "Interventions" also include other processes and actions in the clinical study, such as medical devices, procedures and even non-invasive approaches, making the information more difficult to process.

- **ClinicalTrials.gov**, a database maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH), that publishes studies of the U.S. Clinical Trials Registry in all fifty States in the U.S. and in 210 countries, to collect clinical trials data.

- **Drugs@FDA**, a database with information about most of the drug products approved since 1939, to gather data on FDA-approved drug products.

[5] According to the FDA's drug development process, clinical trials are those involving human beings, whereas pre-clinical trials are those involving animals.

- **Dietary Supplement Label Database**, a database that includes all label information on dietary supplement products in the US.

- **ChemID*plus***, a dictionary database of over 400,000 chemicals, which is used to classify molecular entities and therapeutic biological products.

The NLM Drug Information Portal classifies drugs by therapeutic class, so it is possible to obtain the list of cancer drugs using the "antineoplastic agents" category. In the "antineoplastic agents" list, there were 978 antineoplastic agents. Through the Dietary Supplement Label Database, 27 dietary supplements were identified that were not intended to diagnose, treat, cure or prevent any disease, so they were omitted. The final database contained 518 antineoplastic drugs developed in 42,653 clinical trials.

To improve the matching rate of data between ClinicalTrials.gov and Drugs@FDA, the organisation names were normalised. The details of normalisation are given in section 3.3.2. The ChemID*plus* database was useful when it came to classifying subsamples, as described in section 3.3.3. The software Python 3.7 was used to scrape clinical trial data, FDA approved drug products, information of dietary supplement and MeSH information based on the gateway of the NLM Drug Information Portal to ClinicalTrials.gov, Drugs@FDA, Dietary Supplement Label Database and ChemID*plus* respectively.

3.3.2 Normalisation of organisation names

Organisation names were extracted from ClinicalTrials.gov's field "Sponsor/Collaborators". In the original database, there were 10,601 different organisation names. Given that the field could contain individuals (rather than organisations) and that one organisation could wrongly appear with more than one name, or one name could be wrongly attributed to various organisations, the following three steps to

normalise organisation names were employed, based on Jonnalagadda & Topham (2010).

Step 1. Removing the names of individuals: Some of the clinical trials do not show organisations but individuals (e.g., principal investigators) in the field "Sponsor/Collaborators". To delete records with the names of individuals, a search was conducted into the co-occurrence of names and personal titles: prof.*, M.D.*, MD*, M D *, PhD* and Dr.*. The Name Corpus (http://www.cs.cmu.edu/Groups/AI/util/areas/nlp/corpora/names/) was also used. This is a package that contains a list of 13,484 surnames and 58,257 names (Kantrowitz & Ross, 1994). After these processes, the names of 548 individuals were manually removed.

Step 2. Cleaning strings with geographic information: Some records with incomplete geographic information in the field "Sponsor/Collaborators" had to be deleted. The Geopolitical Entity (GPE) was identified by means of the GeoWorldMap database (https://geobytes.com/freeservices/), which includes 275 country names and 39,484 city names. A total of 2,198 organisation names were retrieved with GPE. However, there were two types of strings with geographic information.

- The first linked the organisation with only one item of geographic information. The location information of these organisations was manually cleaned. For example, the only GPE of "Copenhagen University Hospital, Denmark" is Denmark. The information "Denmark" was removed, and only "Copenhagen University Hospital" was kept.

- The second type linked one organisation to more than one GPE. In this case, the place and organisation names were kept together. For example, "Ministry of Health" could be attributed to more than ten GPEs (e.g., China, Spain, France, Czech Republic, Japan, Republic of Korea, and so on). The location of these organisations was kept; e.g., Ministry of Health, China or Ministry of

Health, France.

Step 3. Resolving synonymy: One major challenge in normalising organisation names is to identify and replace Non Standard Words (NSWs). NSWs can be broadly classified as abbreviations, misspellings and miscellaneous (Sproat et al., 2001). The category "miscellaneous" includes the unconventional word and phrase boundaries, intentional informal spelling, URL and formatting abnormalities. Two types of miscellaneous NSWs are in the database for the study: those with trademark logos like ©, ™, ® or for types of companies like LLC., Ltd. and GmbH.; and those with special alphabets from other languages, such as ó, ç, ñ and so on. The trademark logos and types of companies were removed, and similar English characters were used instead of those from other alphabets. Abbreviations were replaced by their full forms. For example, NIH needed to be replaced by the National Institutes of Health. To resolve the misspellings, OpenRefine was used. This is a powerful tool for working with messy data, to compare string similarity and normalise the different strings as the same organisations if they had less than two different letters, as can be seen in the example given in Table 3.1a. The other major source of misspellings was that some non-English organisations might appear with English translations or original names. To disambiguate these synonyms, each non-English organisation name was translated to English using Google Translate, as illustrated by the example provided in Table 3.1b.

After the organisations had been normalised, the database included 8,738 organisations engaged in clinical trial development on antineoplastic agents.

Table 3.1 Normalised organisation name

a: Normalised organisation name by OpenRefine

Input	Output
National Centre for Parasitology	National Center for Parasitology
National Center for Parasitology	National Center for Parasitology

b: Normalised non-English organisation name by Google Translate

Input	Output
Hanusk Krankenhaus Wien	Hanusch Hospital Vienna
Havenziekenhuis	Port Hospital

3.3.3 Building the sample and subsamples

Since 2005, clinical trials have been required to be registered in ClinicalTrials.gov by the International Committee of Medical Journal Editors before the results are published. Only the clinical trials from 2005 to 2018 were considered for the purposes of the present study, resulting in 491 antineoplastic agents, 7,373 organisations and 39,886 clinical trials. To build the indicators, the data from the drug-clinical trial level (Table 3.2a) was converted into the organisation level (Table 3.2b). Any ongoing clinical trials (see details in section 3.3.4) were also deleted. Finally, a figure of 4,646 observations was in the database.

Table 3.2 Sample level examples

a: Drug-clinical trial level

Drug Name	NCT Number	Sponsor/Collaborators
10-Hydroxycamptothecin	NCT00003735	Children's Oncology Group|National Cancer Institute
Topotecan	NCT00003735	Children's Oncology Group|National Cancer Institute
2-Chloro-3'-deoxyadenosine	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute
Prednisolone	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute
Cladribine	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute
Cytarabine	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute
Fludarabine	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute
Idarubicin	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute
Methylprednisolone Hemisuccinate	NCT00002833	M.D. Anderson Cancer Center|National Cancer Institute

b: Drug-organisation level

Organisation name	Number of clinical trials	Number of drugs
Children's Oncology Group	1	2
National Cancer Institute	2	8
M.D. Anderson Cancer Center	1	6

The robustness of the results will also be tested by distinguishing 3 subsamples: chemical, biomedical and mixed organisations. The chemical organisations (biomedical organisations) only develop molecular entities (therapeutic biological products). The mixed organisations develop both types of drugs. Molecular entity drugs do not contain active moiety and have well-defined structures, whereas therapeutic biological products drugs are generally derived from living material with complex structures, and are thus not usually fully characterised (FDA, 2015). Because molecular entities have well-defined structures, the chemical organisations can make sure they use the same molecular entities in the different stages of clinical trials by analysing the structure of the product. In contrast, therapeutic biological products are sensitive to every minor change in the manufacturing process. Biomedical organisations must stringently control the source

and nature of primary materials and the manufacturing process to make sure therapeutic biological products have the same consistency, quality and purity at different stages of the clinical trials. Furthermore, therapeutic biological products approval requires a special biological license. Mixed organisations have to furnish both types of capabilities to develop drugs.

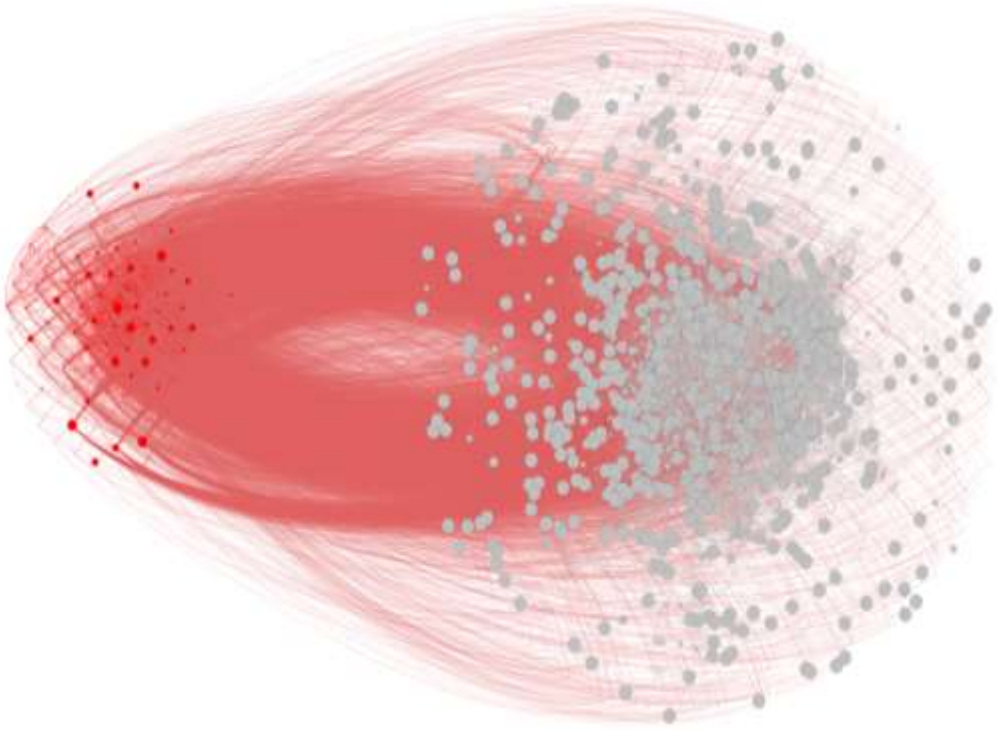
The classification by drug type is based on Medical Subject Headings (MeSH). This is a controlled and hierarchically-organised vocabulary produced by the U.S. National Library of Medicine, used for indexing, cataloguing and searching for biomedical and health-related information. There are 326 molecular entities and 165 therapeutic biological products in the database for the present study. Matching the type of drugs and organisations yields 2,237 chemical organisations, 453 biomedical organisations and 1,956 mixed organisations.

Table 3.3 lists the top 10 organisations in cancer drugs development. The typical top 10 organisation is a *Public Research Organisation.* The U.S. National Cancer Institute ranks first, with 268 drugs. Every organisation has achieved success in cancer drug development at least once, with the exception of the Dana-Farber Cancer Institute. However, the highest success rate corresponds to *Companies* — with Pfizer coming first, having a success rate of over 70%. The National Cancer Institute developed the highest number of radical drugs. Since data was collected from U.S. Clinical Trials Registry, most of the organisations come from the U.S., except Novartis and Roche, located in Switzerland, who also score highly in success rate.

Table 3.3 Top 10 organisations in cancer clinical trials from 2005 to 2018

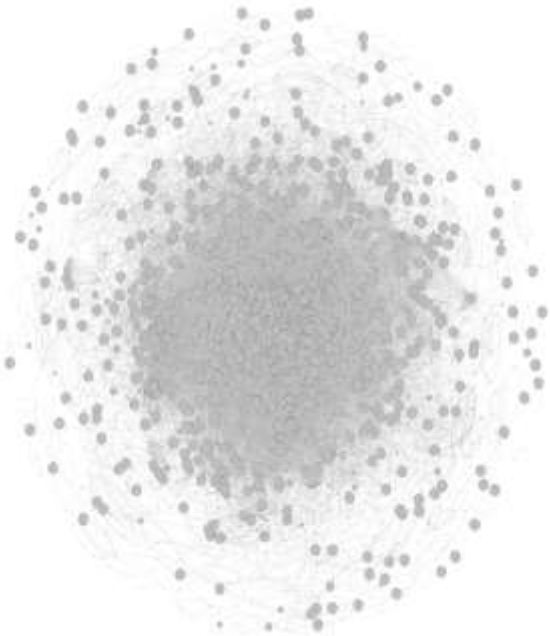
Rank	Organisation name	Number of cancer drugs	Number of successful drugs	Number of ongoing drugs	Number of failed drugs	Number of radical drugs	Success rate	Organisation Type	Nationality
1	National Cancer Institute	268	16	198	54	16	22.86%	Public Research Organisation	U.S.
2	MD Anderson Cancer Center	179	4	154	21	1	16.00%	Public Research Organisation	U.S.
3	University of California	148	17	103	28	1	37.78%	Higher education	U.S.
3	National Institutes of Health Clinical Center	148	6	111	31	2	16.22%	Public Research Organisation	U.S.
5	Memorial Sloan Kettering Cancer Center	144	2	112	30	1	0.06%	Public Research Organisation	U.S.
6	Merck	143	23	100	20	0	53.49%	Company	U.S.
7	Novartis	139	39	81	19	6	67.24%	Company	Switzerland
8	Dana-Farber Cancer Institute	137	0	110	27	0	0.00%	Public Research Organisation	U.S.
9	Roche	127	38	67	22	2	63.33%	Company	Switzerland
10	Pfizer	126	40	70	16	4	71.42%	Company	U.S.

Figure 3.2 shows the co-operation network of organisations. The co-operation networks were built according to the field "Sponsor/Collaborators" in ClinicalTrials.gov. If Organisation A co-operates in at least one clinical trial with Organisation B, there is a co-operation relationship between them. The red nodes are the organisations that developed at least one radical drug. The grey nodes are the organisations that only developed incremental drugs. The node size depends on the success rate: bigger nodes mean a higher success rate, smaller nodes a lower rate. The links between nodes are the co-operation relationships between organisations: the red links are the co-operation relationships with radical organisations; the grey links are not with radical organisations. Figure 3.2a reveals that most organisations only develop incremental drugs. There are more successful organisations with incremental drug development than with radical drug development, and the success rates are higher in organisations with incremental drug development than in those with radical drug development (see Figure 3.2a). The organisations with radical drug development co-operate closely with other organisations with radical drug development (see Figure 3.2b and 3.2c), and they also build co-operation relationships with organisations with incremental drug development (see Figure 3.2a).



a. Co-operation network of all organisations organizations

b. Co-operation network of organisations with radical drug development



c. Co-operation network of organisations with incremental drug development

Figure 3.2 Co-operation network

3.3.4 Variables

The dependent variable is *Success Rate*. It is considered that an organisation achieves success in a given drug development if the FDA approves the corresponding clinical trial in Drugs@FDA, in the case of drug firms; or if it enters into Phase IV in ClinicalTrials.gov (indicating that the drug is on the market), in the case of other organisations (Willmann et al., 2008).[6] When it is not observed whether a drug achieves success during the period, a 5-year threshold is set for phase I and III, and a 6-year threshold for phase II to indicate *Failed* or *Ongoing* (based on Danzon et al., 2005). For a given organisation, if one drug has completed phase I or III clinical trials before 2014 or completed phase II before 2013 and no further action is reported, it is assumed assume that the organisation failed in this drug. Otherwise, it is assumed this drug is still ongoing for this company. The calculation of the *Success of Drug Development* is as follows:

$$Succes\ Rate_i = \frac{Number\ of\ Successful\ Drugs_i}{Number\ of\ Successful\ Drugs_i + Number\ of\ Failed\ Drugs_i}$$

where $Success\ Rate_i$ is the success rate of organisation i. $Number\ of\ Successful\ Drugs_i$ is the

[6] The reason for considering both events (FDA approval or entering Phase IV) is as follows: in the clinical trial workflow, there are four phases. In general, Phases I to III test the safety, dosage, efficacy, side effects and adverse reactions of a drug on a limited number of volunteers or people with the disease/condition, which may take 3 to 8 years. If a drug passes Phase III, the sponsor organisation can apply to the FDA to launch the drug on the market. If the FDA approves it, it scores 1 in the dependent variable. However, the Drugs@FDA database only contains information about companies and not about other organisations. To measure the success of drug development in the case of other organisations, entry into Phase IV clinical trials is used. Only drugs approved by FDA can enter Phase IV, so entry into Phase IV implies success of approval and it also scores 1 in the dependent variable. Phase IV involves clinical trials about the safety and efficacy of drugs in huge amounts of patients. This method has one limitation, however: if a drug developed jointly by a company and another organisation is approved by the FDA but did not enter Phase IV, the company would score 1 in success, but the other organisation would score 0; therefore, the success of other organisations is underestimated. However, previous research calculated success rates of 24.5% in oncology (DiMasi & Grabowski, 2007), which is similar to the 24.8% success rate of the present study, so this underestimation does not seem to affect the results significantly.

number of successful drugs in organisation i. $Number\ of\ Failed\ Drugs_i$ is the number of failed drugs in organisation i.

The first independent variable is *Radicalness*. For a given drug, if an organisation is the first to develop this drug based on the start year of clinical trials, it is considered that this organisation has developed a radical drug.[7] A new drug is one with a new molecular entity or a new therapeutic biological product (FDA, 2015). All clinical trials were tracked for each drug on ClinicalTrials.gov to confirm the number of radical drugs for a given organisation. The calculation of *Radicalness* is as follows:

$$Radicalness_i = \frac{Number\ of\ Radical\ Drugs_i}{Number\ of\ Drugs_i}$$

where i represents an organisation. $Number\ of\ Radical\ Drugs_i$ is the number of radical drugs in organisation i. $Number\ of\ Drugs_i$ is the total number of drugs in organisation i.

The second independent variable is *Density*. *Density* is used to describe the cohesion of an ego network. It measures the actual number of existing links between actors compared to the possible number of links between actors in the ego network. The calculation of *Density* is as follows:

$$Density_i = \frac{m_i}{n_i(n_i - 1)/2}, i \neq i, j$$

Where m_i is the number of links in company i's ego network, and n_i is the number of organisations in company i's ego network.

The model also verifies the effects of some organisational characteristics, the definitions of which are presented in Table 3.4. *Degree centrality*, *Closeness centrality* and *Diversity of co-operators* verify the

[7] If an organisation develops the same drug, but in a later clinical trial, it is considered to be an incremental drug development; e.g. changing the method of administration from oral to intravenous means.

structure of co-operation networks. *Number of drugs* is a proxy for organisation size in terms of drug development. *Year* takes into account institutional changes in drug development in time. *Ratio of clinical trials* considers the clinical experience of drug development. The *% children* and *% one gender only* elements reflect tests for special cancers which apply to specific groups; for example, neuroblastoma (a common cancer in children under 5 years of age), prostate cancer for males or cervical cancer for females. Most organisations test drugs to cure the diseases of both male and female adults. *Funding sources* control the effects of the funding support. *Sectors of performance* represent the type of organisation.

Table 3.4 Variable definitions and descriptive statistics (n=4646)

Variable name	Description
Dependent variable	
Success rate	The percentage of successful drugs of all drugs for the given organisation.
Independent variables	
Radicalness	The percentage of radical drugs of all drugs for the given organisation.
Density	Density centrality of the given organisation in the ego co-operation network.
Control variables	
Degree centrality	Degree centrality of the given organisation in the co-operation network.
Closeness centrality	Closeness centrality of the given organisation in the co-operation network.
Diversity of co-operators	Diversity of co-operators of the given organisation.
Number of drugs	The number of drugs for the given organisation (standardised).
Year	The average year of clinical trials for the given organisation (ln).
Ratio of clinical trials	The number of clinical trials divided by the number of drugs for the given organisation.
% children	The percentage of clinical trials with children for the given organisation.
% one gender only	The percentage of clinical trials with only males or females for the given organisation.
Funding source	
NIH	The percentage of clinical trials funded by U.S. National Institutes of Health for the given organisation.
Other U.S. Fed	The percentage of clinical trials funded by Other U.S. Federal Government (including Food and Drug Administration, Centres for Disease Control and Prevention or U.S. Department of Veterans Affairs) for the given organisation.
Industry	The percentage of clinical trials funded by pharmaceutical and device companies for the given organisation.
Other funding	The percentage of clinical trials funded by Other Sources (including individuals, universities and community-based organisations) for the given organisation.
Sector of performance	
Company	1 if the organisation is a company, 0 otherwise.
Hospital	1 if the organisation is a hospital, 0 otherwise.
Higher education	1 if the organisation is a higher educational institution (include university, college, and so on), 0 otherwise.
Public research organisation	1 if the organisation is a public research organisation, 0 otherwise.
Other organisation	1 if the organisation is another organisation, 0 otherwise.

3.4 Descriptive statistics

This chapter focuses on the impacts of radicalness and network density on the success of drug. In this section, we display the descriptive statistics of our sample and the variables. The average value of *Success Rate* is 24.8 %, which is consistent with other research (e.g. Crispeels et al., 2018).

3.4.1 Descriptive statistics of key variables

Table 3.5 shows the descriptive statistics of the variables. The average value of *Radicalness* is remarkably low (0.005). Consequently, this means that the immense majority of clinical trials made by organisations concern incremental developments. The average value of *Density* is 0.451, which indicates that almost half of organisations always co-operate together to develop drugs in an ego network.

Table 3.5 Descriptive statistics of key variables (n=4646)

Role of variable	Variable name	Mean	Std. Dev.	Min	Max
Dependent variable	*Success rate*	0.248	0.391	0.000	1.000
Independent variables	*Radicalness*	0.005	0.056	0.000	1.000
	Density	0.451	0.410	0.000	1.000
Control variables	*Degree centrality*	0.002	0.005	0.000	0.087
	Closeness centrality	0.211	0.114	0.000	0.439
	Diversity of co-operators	0.496	0.333	0.000	1.000
	Number of drugs	8.737	16.086	1.000	268
	Year	1.454	0.523	0.000	3.219
	Ratio of clinical trials	0.960	0.825	0.063	14.437
	% children	0.142	0.302	0.000	1.000
	% one gender only	0.165	0.311	0.000	1.000
	NIH	0.021	0.084	0.000	0.945
	Other U.S. Fed	0.013	0.081	0.000	1.000
	Industry	0.261	0.328	0.000	1.000
	Other funding	0.705	0.335	0.000	1.000
	Company	0.296	0.457	0.000	1.000
	Hospital	0.283	0.450	0.000	1.000
	Higher education	0.142	0.349	0.000	1.000
	Public research organisation	0.170	0.376	0.000	1.000
	Other organisation	0.110	0.312	0.000	1.000

The descriptive statistics of control variables shows that organisations develop 8.7 drugs on average. The average value of *Ratio of clinical trials* is less than 1, which means most organisations have the clinical experience to test combinations of more than one drug in one clinical trial. Regarding *funding sources*, because there are a large number of non-profit organisations sponsoring clinical trials — e.g., topic-oriented foundations and disease-specific societies, especially orphan drugs clinical trials (Davies et al., 2017) — most drug development organisations receive funding from *Other sources*. A quarter of the funding comes from industry and only a small amount from NIH and the U.S. Federal Government.

Figure 3.3 displays the distribution of organisations by type. The majority of organisations are companies (30%) or hospitals (28%). This is consistent with the intuition that companies have more interest to participate in clinical trials, because they hope to develop new drugs to improve financial returns, and hospitals are the necessary places to develop clinical trials.

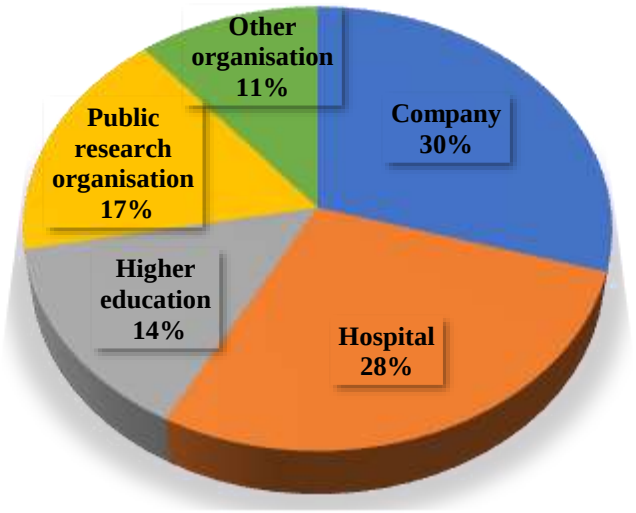


Figure 3.3 The distribution of organisations by type

3.4.2 Descriptive statistics by organisation type

Figure 3.4 displays the average success rate of each type of organisation respectively. The horizontal red line is the average success rate of drug development (25%). Public research organisations (32%) and hospitals (31%) have much higher success rates than the average value. Although companies participate actively in clinical trials, the success rate of companies is remarkably low (19%).

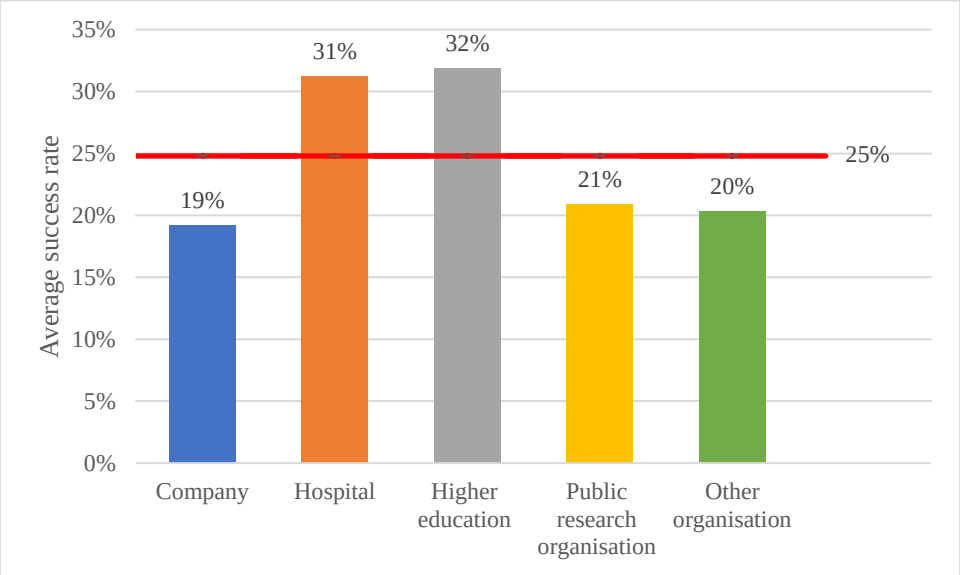


Figure 3.4 Success rate by type of organisation

Figure 3.5 displays the average radicalness of each type of organisation and the horizontal red line is the average radicalness (0.005). The radicalness is very low for all types of organisations, which means organisations tend to develop incremental drugs instead of radical drugs to avoid risks. Only the company's radicalness (0.010) is higher than the average value, which very likely means the company is more aware about how to develop radical drugs.

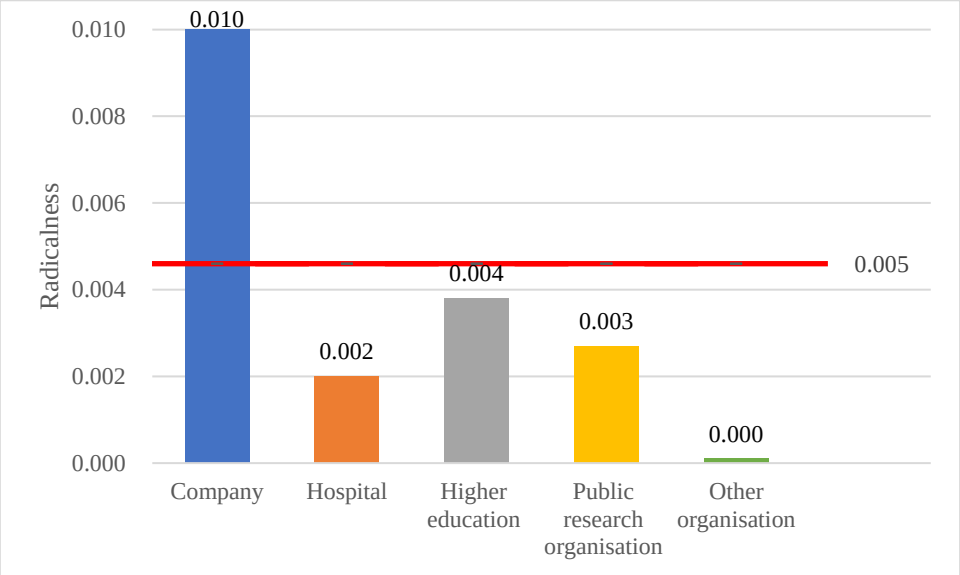


Figure 3.5 The radicalness of each type of organisation

Figure 3.6 shows the distribution of average network density for each type of organisation. The horizontal red line is the average value of network density (0.45). The network density of hospital is the highest (0.55), and the network density of company is the lowest (0.35). In line with intuition, the other types of organisations have to cooperate with hospitals to develop clinical trials, since hospitals always provide a place to support clinical trials. A large number of cooperators of hospitals causes the dense cooperation network of hospitals. In contrast, companies avoid cooperating with many members to decrease the risks of core technology disclosure, so companies are always embedded in sparse networks.

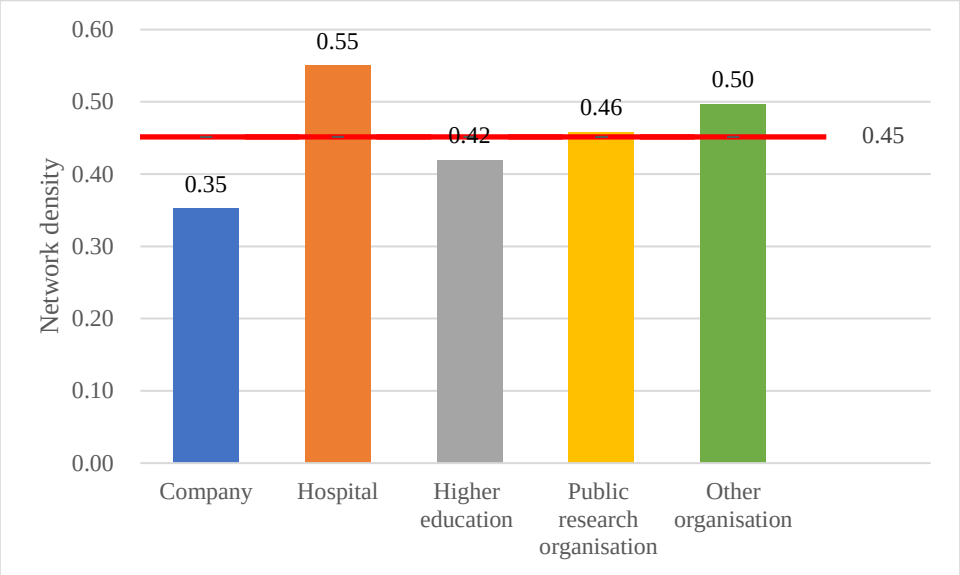


Figure 3.6 The network density for each type of organisation

Figure 3.7 displays the funding sources of each type of organisation. Let us recall that there are four funding sources, including NIH, the U.S. Federal Government, Industry, and Other sources (such as individuals, universities, and community-based organisations). The percentage of NIH and U.S. Federal Government, two typical public funding sources, are remarkably low for all types of organisations. Companies get more funding from the industry (60%), which is in line with the intuition that companies always use their own funding to develop clinical trials. The rest of organisations get funding mainly from Other sources.

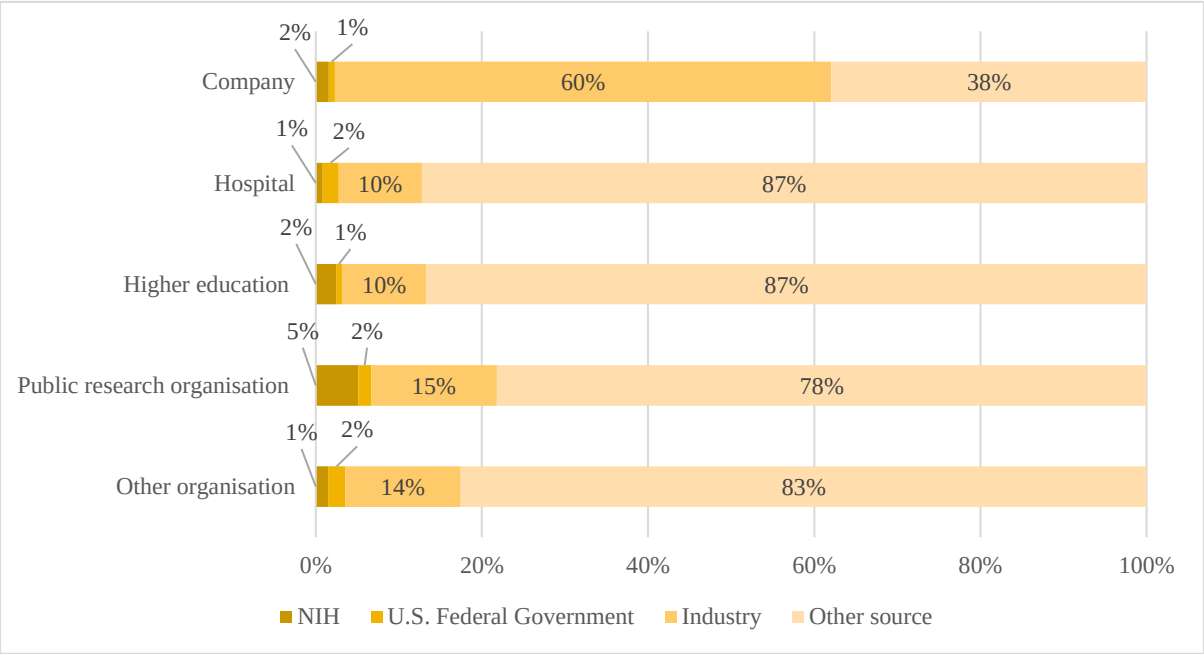
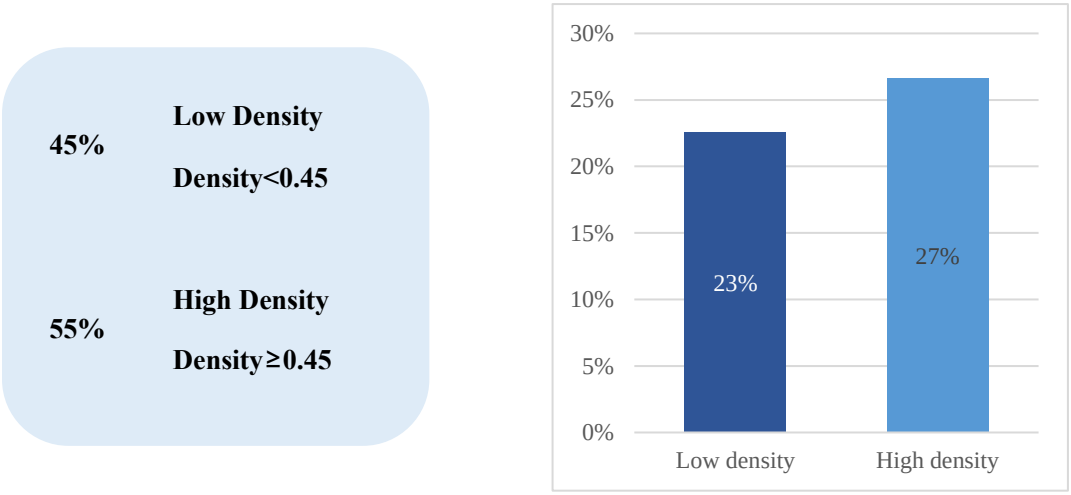


Figure 3.7 Funding sources by type of organisation

3.4.3 Descriptive statistics by network density

This study also explores the moderating role of network density on the relationship between radicalness and success of drug development. For descriptive purposes, we set the average value of network density (0.45) as the threshold of low and high density, and display the percentage of observations and success rate in low and high density networks in Figure 3.8. Figure 3.8a shows the percentage of observations in low and high density networks. There are more observations in high density networks (55%) than in low density networks. Figure 3.8b displays the success rate in low density and high density networks. The success rate is a little bit lower in low density networks (23%) than in high density networks (27%).



a. The percentage of observations in low and high density network

b. The success rate in low and high density network

Figure 3.8 The percentage of observations and the success rate in low and high density network

3.4.4 Descriptive breakdown by chemical, biomedical and mixed organisations subsamples

As mentioned above, the sample contains chemical, biomedical and mixed organisations. As their development follows different dynamics, a distinction will be made between the three types in order to perform a robustness check. Table 3.6 breaks down the descriptive statistics of the variables for the chemical, biomedical and mixed organisation subsamples. The sample contains 48.15% chemical, 9.75% biomedical and 42.10% mixed organisation subsamples. The *Success rate* of chemical drug organisations (0.285) is slightly higher than the others; however, they differ considerably in that biomedical organisations develop more radical drugs than the others. The appearance of new biotech provides some innovative paths for developing drugs; thus, the biomedical organisations develop more radical drugs. Compared with others, the networks of the mixed organisations are more diverse and less dense. Mixed organisations develop the

greatest number of drugs. Biomedical organisations develop more clinical trials than the others. Chemical organisations rely more on *Other U.S. Fed* and *Other funding* than the others. The distributions are fairly similar in terms of % *children*, *% one gender only,* and *Sector of performance.*

Table 3.6 Descriptive statistics of variables: chemical, biomedical and mixed organisations subsamples

	Chemical organisations (n=2237)				**Biomedical organisations (n=453)**				**Mixed organisations (n=1956)**			
Variable name	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
Success rate	0.285	0.438	0.000	1.000	0.214	0.408	0.000	1.000	0.213	0.319	0.000	1.000
Radicalness	0.003	0.047	0.000	1.000	0.018	0.128	0.000	1.000	0.004	0.032	0.000	0.667
Density	0.471	0.461	0.000	1.000	0.471	0.487	0.000	1.000	0.424	0.317	0.000	1.000
Degree centrality	0.001	0.002	0.000	0.011	0.001	0.001	0.000	0.006	0.004	0.007	0.000	0.087
Closeness centrality	0.175	0.116	0.000	0.330	0.176	0.114	0.000	0.299	0.261	0.090	0.000	0.439
Diversity of co-operators	0.491	0.365	0.000	1.000	0.431	0.375	0.000	1.000	0.516	0.277	0.000	1.000
Number of drugs	2.504	2.339	1.000	20.00	1.267	0.566	1.000	4.000	17.595	21.738	2.000	268
Year	1.358	0.593	0.000	3.219	1.326	0.541	0.000	2.773	1.592	0.383	0.000	3.219
Ratio of clinical trials	0.973	0.814	0.100	12.00	1.143	0.762	0.025	10.00	0.903	0.845	0.063	14.437
% children	0.166	0.349	0.000	1.000	0.108	0.306	0.000	1.000	0.122	0.234	0.000	1.000
% one gender only	0.215	0.383	0.000	1.000	0.046	0.205	0.000	1.000	0.135	0.212	0.000	1.000
NIH	0.014	0.074	0.000	0.550	0.008	0.056	0.000	0.500	0.031	0.097	0.000	0.945
Other U.S. Fed	0.020	0.100	0.000	1.000	0.007	0.066	0.000	1.000	0.008	0.056	0.000	1.000
Industry	0.254	0.353	0.000	1.000	0.284	0.357	0.000	1.000	0.232	0.288	0.000	1.000
Other funding	0.712	0.359	0.000	1.000	0.701	0.360	0.000	1.000	0.699	0.297	0.000	1.000
Company	0.325	0.468	0.000	1.000	0.351	0.478	0.000	1.000	0.251	0.433	0.000	1.000
Hospital	0.269	0.444	0.000	1.000	0.258	0.438	0.000	1.000	0.304	0.460	0.000	1.000
Higher education	0.104	0.305	0.000	1.000	0.110	0.313	0.000	1.000	0.192	0.394	0.000	1.000
Public research organisation	0.170	0.376	0.000	1.000	0.168	0.374	0.000	1.000	0.171	0.376	0.000	1.000
Other organisation	0.132	0.339	0.000	1.000	0.113	0.316	0.000	1.000	0.083	0.276	0.000	1.000

3.5 Results

In this section, we test the effects of radicalness and network density on the success of drug development. Table 3.7 displays the correlations of variables. According to Table 4.8, most of the correlations between variables are low, except the correlation between Degree *centrality* and *Number of drugs* (0.799) and the correlation between *Industry* and *Company* (0.673). Additionally, the variance inflation factor (VIF) was applied to test multicollinearity. The VIF scores were calculated for each predictor variable, and all scores were below 3.55, indicating that multicollinearity was not an issue in the model (Neter et al., 1996).

Table 3.7 Correlations of the variables in full samples

Variable name	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. *Success rate*																	
2. *Radicalness*	**-0.045**																
3. *Density*	**-0.050**	**-0.025**															
4. *Degree centrality*	**0.064**	0.008	**0.042**														
5. *Closeness centrality*	**-0.047**	0.009	**0.457**	**0.369**													
6. *Diversity of co-operators*	**-0.046**	-0.011	**-0.118**	**0.061**	**-0.359**												
7. *Number of drugs*	-0.018	0.001	**-0.087**	**0.799**	**0.348**	**0.110**											
8. *Year*	**-0.176**	-0.007	**0.230**	**0.174**	**0.335**	**-0.044**	**0.189**										
9. *Ratio of clinical trials*	**0.151**	0.124	**-0.138**	**0.238**	**-0.021**	**0.068**	**0.177**	**-0.151**									
10. *% children*	**0.046**	0.019	**0.131**	0.016	**0.075**	**0.027**	-0.011	**0.050**	-0.021								
11. *% one gender only*	-0.014	-0.004	**-0.025**	**-0.022**	-0.020	**0.048**	-0.017	**-0.049**	**0.037**	**-0.097**							
12. *NIH*	**-0.094**	-0.008	**0.085**	**0.112**	**0.195**	**0.065**	**0.192**	**0.112**	**0.040**	**0.090**	0.001						
13. *Other U.S. Fed*	0.005	-0.010	**0.034**	0.013	**0.045**	**0.045**	**-0.031**	0.009	0.007	-0.008	**0.078**	0.008					
14. *Industry*	**-0.132**	**0.056**	**-0.292**	**-0.111**	**-0.200**	**0.115**	**-0.032**	**-0.178**	**0.196**	**-0.175**	-0.000	**-0.085**	**-0.079**				
15. *Company*	**-0.093**	**0.050**	**-0.222**	**-0.153**	**-0.187**	**0.030**	**-0.089**	**-0.151**	**0.170**	**-0.130**	-0.003	**-0.033**	**-0.054**	**0.673**			
16. *Hospital*	**0.103**	**-0.029**	**0.189**	**0.163**	**0.096**	**-0.082**	0.019	**0.067**	**-0.119**	0.011	**-0.042**	**-0.083**	**0.046**	**-0.345**	**-0.449**		
17. *Higher education*	**0.073**	-0.005	-0.020	**0.096**	**0.032**	**0.069**	**0.120**	**-0.027**	-0.011	**0.037**	0.017	0.014	-0.022	**-0.196**	**-0.265**	**-0.223**	
18. *Public research organisation*	**-0.046**	-0.016	**0.028**	**-0.039**	**0.037**	0.017	**0.023**	0.089	-0.039	0.039	0.030	0.125	0.014	-0.167	**-0.314**	**-0.265**	**-0.157**

Note. The correlation estimates in bold are significant at the 0.05 level.

3.5.1 Main results

Since *Success rate*, the dependent variable, ranges from 0 to 1, a fractional probit model is employed for the estimations. Table 3.8 presents the various models: in Model 1, only the control variables are included; Model 2 tests the impacts of *Radicalness* and *Density*; Model 3 tests the nonlinear effect of *Density*; Model 4 tests the moderating role of *Density* on the relationship between radicalness and success rate; and Model 5 includes all variables.

The coefficients of *Radicalness* are negative and significant in Models 2–5. This means that radical drug development is less likely to succeed, which supports ***Hypothesis 1***. In Models 3 and 5, the coefficient of *Density* squared is negative and significant. This means that increasing density gives organisations a greater likelihood of success; however, over a threshold, density decreases the success rate, which supports ***Hypothesis 2***. In Models 4 and 5, the coefficient of *Radicalness*Density* is positive and significant, which means a dense network is beneficial to radical drug development, supporting ***Hypothesis 3***; i.e., the benefit of accessing external knowledge through networks compensates the cost of coordinating partners in radical drug development, which depends to a great extent on external knowledge; but this is not the case for incremental drug development, which relies less on external knowledge.

Table 3.8 Fractional probit model estimation of success rate of drug development

	(1)	(2)	(3)	(4)	(5)	(6) Low-Density	(7) High-Density
Radicalness (H1)		-6.27*	-5.76*	-10.64***	-9.48***	-8.53***	0.40***
		(3.42)	(3.23)	(4.12)	(3.66)	(3.31)	(0.10)
Density		0.11*	0.73***	0.12*	0.72***	0.57**	-0.40**
		(0.06)	(0.20)	(0.06)	(0.20)	(0.28)	(0.16)
Density^2 (H2)			-0.57***		-0.55***		
			(0.18)		(0.18)		
*Radicalness*Density (H3)*				7.12*	6.08*		
				(3.91)	(3.32)		
Degree centrality	31.15***	31.58***	30.25***	32.07***	30.70***	19.36***	70.62***
	(6.05)	(5.00)	(4.87)	(4.94)	(4.81)	(6.10)	(12.98)
Closeness centrality	-0.64***	-0.29	-0.61***	-0.29	-0.59***	-0.64*	-0.59
	(0.22)	(0.19)	(0.22)	(0.19)	(0.22)	(0.35)	(0.49)
Diversity of co-operators	-0.28***	-0.24***	-0.28***	-0.24***	-0.28***	-0.21**	-0.68***
	(0.07)	(0.05)	(0.06)	(0.05)	(0.06)	(0.09)	(0.13)
Number of drugs	-1.86***	-1.92***	-1.93***	-1.88***	-1.90***	-2.09***	-4.09***
	(0.47)	(0.40)	(0.40)	(0.40)	(0.39)	(0.56)	(0.97)
Year	-0.41***	-0.34***	-0.35***	-0.34***	-0.35***	-0.22***	-0.66***
	(0.04)	(0.03)	(0.04)	(0.03)	(0.04)	(0.05)	(0.07)
Ratio of clinical trials	0.24***	0.20***	0.21***	0.20***	0.21***	0.30***	0.23***
	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.06)
% children	0.13**	0.10**	0.10**	0.10**	0.10**	0.12	0.17**
	(0.06)	(0.05)	(0.05)	(0.05)	(0.05)	(0.11)	(0.09)
% one gender only	-0.05	-0.03	-0.02	-0.03	-0.02	-0.06	-0.00
	(0.07)	(0.05)	(0.05)	(0.05)	(0.05)	(0.08)	(0.11)
NIH	-1.57***	-1.25***	-1.26***	-1.24***	-1.24***	-0.98**	-1.88***
	(0.30)	(0.24)	(0.24)	(0.23)	(0.24)	(0.41)	(0.44)
Other U.S. Fed	-0.00	0.02	0.05	0.02	0.05	0.01	0.08
	(0.23)	(0.18)	(0.19)	(0.18)	(0.18)	(0.33)	(0.35)
Industry	-0.64***	-0.56***	-0.57***	-0.56***	-0.56***	-0.49***	-0.79***
	(0.09)	(0.08)	(0.08)	(0.08)	(0.08)	(0.11)	(0.15)
Company	0.10	0.10	0.10	0.10	0.10	0.01	0.18
	(0.08)	(0.06)	(0.06)	(0.06)	(0.06)	(0.12)	(0.12)
Hospital	0.31***	0.22***	0.20***	0.21***	0.20***	0.41***	0.16
	(0.07)	(0.06)	(0.06)	(0.06)	(0.06)	(0.10)	(0.11)
Higher education	0.35***	0.26***	0.25***	0.26***	0.24***	0.37***	0.27**
	(0.08)	(0.07)	(0.07)	(0.06)	(0.06)	(0.10)	(0.12)
Public research organisation	0.09	0.06	0.05	0.06	0.05	0.12	0.02
	(0.08)	(0.06)	(0.06)	(0.06)	(0.06)	(0.11)	(0.12)
Constant	-0.12	-0.15*	-0.11	-0.15*	-0.12	-0.46***	0.75***
	(0.10)	(0.09)	(0.09)	(0.08)	(0.09)	(0.14)	(0.26)
χ^2	485.42	416.12	430.37	417.07	432.65	259.43	768.68
P-value	0.00	0.00	0.00	0.00	0.00	0.00	0.00
N	4646	4646	4646	4646	4646	2,323	2,323

*Note. Robust standard errors in parentheses; * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. No collinearity according to VIF.*

To capture the intuition behind the interaction variable, in Models 6 and 7 the figure of 0.3715 (the median of *Density*) is set as the threshold for *Density*, and to test the effect of radicalness and density on success rate in both low and high densities. In Model 6, the coefficient of *Density* is positive and significant, whereas in Model 7, the coefficient of *Density* is negative and significant. This result means that in the low-density network, organisations receive more benefits than cost; thus, increasing network density provides more likelihood of achieving success. However, with the increasing density, the cost of co-ordinating co-operators also increases. Therefore, over the threshold, organisations receive less benefits than their investment costs, and the density plays a negative role on the success rate.

The coefficient of *Radicalness* is negative and significant in Model 6, whereas it is positive and significant in Model 7. This means that in the low-density network, there is not enough knowledge or resources to support radical drug development; thus, radical drug development decreases the success rate. However, in a high-density network, radical organisations receive more knowledge and resources to support new drugs development; thus radical drug development increases the success rate.

Figure 3.9 depicts the moderating role of density. There is a marginal negative impact of the radicalness on the success rate in the low-density co-operation network, but in the high-density network, the marginal effect of radicalness on success rate is positive. This indicates that in the low-density network, there is not enough knowledge and resources to support radical drug development, but radical organisations receive more knowledge and resources to develop new drugs successfully in a dense network, supporting ***Hypothesis 3***.

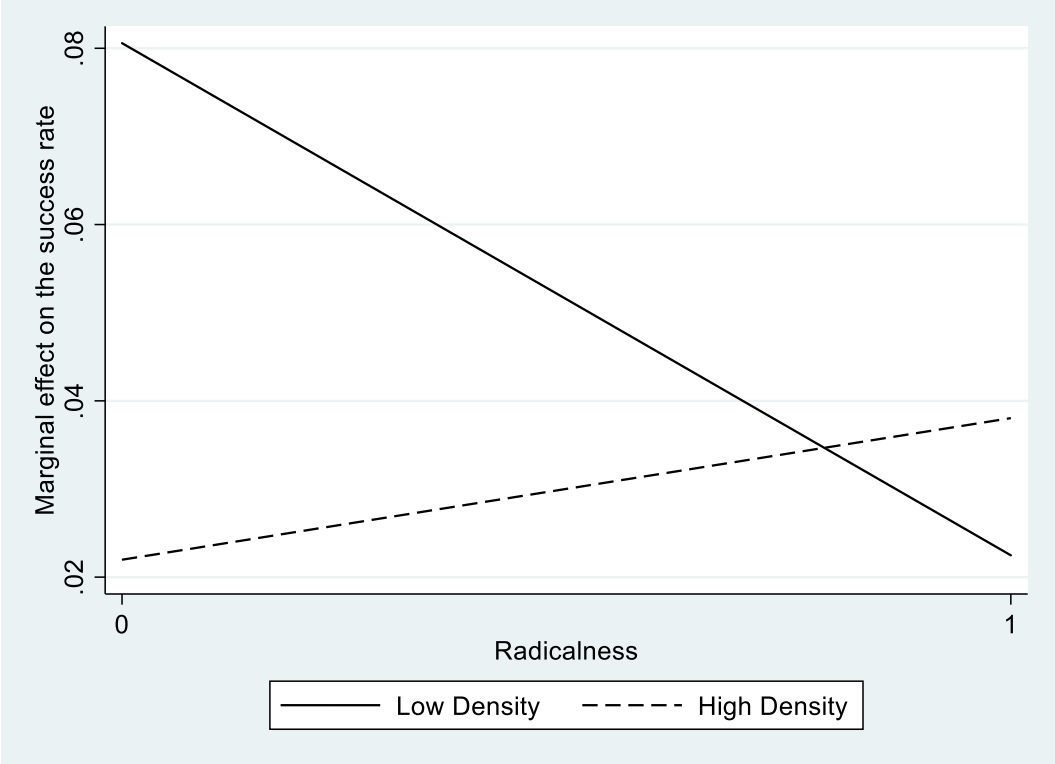


Figure 3.9 Marginal effect of radicalness on the success rate

Regarding the control variables in Table 3.8, the coefficients of *Degree centrality* reflect that more co-operators mean higher success rates, whereas *Closeness centrality* decreases the success rate. The coefficients of *Diversity of co-operators* reveal that it is beneficial to co-operate with similar types of co-operators. Increasing the *Number of drugs* hinders the success rate, very likely because most organisations abandon some drugs during the development process. The coefficient of *Ratio of clinical trials* shows that more clinical experience improves the success rate of drug development. Among types of organisations, *Hospital* and *Higher education* tend to be the most successful. This is perhaps because most drug developments are sponsored by companies (Angell, 2008), which tend to outsource the task to contract research organisations (Vogel, 2007), including hospitals, universities and public research organisations. Hospitals have more clinical practice and are necessary places for conducting clinical trials, so drug

development relies on their support. Although both higher education and public research organisations provide knowledge to develop drugs, higher education organisations have more connections with hospitals, so they could also provide some clinical experience on side effects. In contrast, the knowledge of the public organisation is more basic, such as pharmacological action, pharmacokinetics and toxicology, which are useful in selecting pre-clinical candidate compounds, but are not so useful when it comes to resolving side effects in clinical trials.

3.5.2 Robustness test

The sample is broken down to compare the results of chemical, biomedical and mixed drug organisations in Table 3.9. *Radicalness* plays a negative and significant role in the success rate in all subsamples, which means all kinds of organisations developing more radical drugs encounter more risks and have a lower likelihood of achieving success. The relationship between *Density* and *Success rate* follows an inverted U-shape in biomedical and mixed organisations but not in chemical organisations. The reason for this may be that only the biomedical and mixed organisations require knowledge and resources to decrease the risks of biomedical development, as biomedical sources are living materials with complex structures that are highly sensitive to the environment; therefore, coordinating and managing the co-operation to acquire external knowledge and resources is particularly important. The coefficients of *Radicalness*Density* are positive and significant in all subsamples, which means the network density inverts the negative effect of radical drug development on success for every kind of organisation.

Table 3.9 Fractional probit model estimation of success rate of drug development in chemical, biomedical and mixed organisation subsamples

	Chemical organisations	**Biomedical organisations**	**Mixed organisations**
Radicalness (H1)	-10.01***	-15.46***	-19.84***
	(0.33)	(4.65)	(5.68)
Density	0.41	1.72***	0.83***
	(0.38)	(0.31)	(0.29)
Density² (H2)	-0.45	-0.94***	-0.60**
	(0.35)	(0.24)	(0.29)
*Radicalness*Density* (H3)	4.73***	17.91***	14.28**
	(1.73)	(5.48)	(6.75)
Degree centrality	70.23***	-7.04	30.22***
	(17.93)	(6.02)	(5.12)
Closeness centrality	-0.73**	0.20	-0.69*
	(0.35)	(0.15)	(0.37)
Diversity of co-operators	-0.29***	-0.06	-0.36***
	(0.09)	(0.04)	(0.10)
Number of drugs	-0.95	5.73	-1.36***
	(3.09)	(4.33)	(0.42)
Year	-0.37***	-0.05	-0.40***
	(0.05)	(0.03)	(0.10)
Ratio of clinical trials	0.27***	0.04	0.20***
	(0.05)	(0.03)	(0.04)
% children	0.06	0.00	0.27***
	(0.07)	(0.01)	(0.10)
% one gender only	-0.14*	-0.12	0.26**
	(0.07)	(0.08)	(0.12)
NIH	-1.70***	-0.44	-0.89***
	(0.49)	(0.49)	(0.30)
Other U.S. Fed	-0.18	0.10	0.28
	(0.25)	(0.09)	(0.38)
Industry	-0.81***	-0.05	-0.28**
	(0.12)	(0.05)	(0.13)
Company	0.12	-0.00	0.16
	(0.10)	(0.02)	(0.11)
Hospital	0.25***	0.00	0.28***
	(0.09)	(0.02)	(0.09)
Higher education	0.21**	0.02	0.34***
	(0.10)	(0.02)	(0.10)
Public research organisation	0.09	-0.01	0.05
	(0.09)	(0.02)	(0.10)
Constant	0.03	-0.79***	-0.25
	(0.13)	(0.10)	(0.18)
χ^2	15871.12	5790.04	206.28
P-value	0.00	0.00	0.00
N	2237	453	1956

*Note. Robust standard errors in parentheses; * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. No collinearity according to VIF*

The coefficients of *Degree centrality* are positive and significant in chemical and mixed organisations. The coefficients of *Number of drugs* are negative and significant only for mixed organisations. The size, sign and significance of other coefficients are similar to the full sample and between subsamples.

3.6 Conclusions, implications and future research

3.6.1 Conclusions

New drug development presents a dilemma in that more than 90% of prospective medicines fail during the process of their development, especially antineoplastic agents. This research has attempted to raise understanding of how to improve the success rate of drug development according to the nature of the drug development (radical or incremental) and one property of research co-operation networks: their density. Drawing on 39,886 clinical trials in the oncology area from 2005 to 2018, research co-operation networks of clinical trials were built for 4,646 organisations and the relationships between success, radicalness and network density were investigated. It was found that radical drug developments have less likelihood of achieving success because they demand more innovative knowledge and their accompanying clinical trials entail more risks. Co-operation networks are necessary external sources for acquiring knowledge, which also decrease the risks in drug development; however, organisations also face the cost of coordinating network members to make drug development effective. The external knowledge in a denser network promotes the success rate within a threshold; however, beyond that threshold, the efforts involved in coordinating network members decrease the success rate. Although radical drug development has a lower likelihood of achieving success, the dense network improves its success rate because radical organisations acquire more knowledge and resources in denser networks.

A further distinction is made between three subsamples of chemical, biomedical and mixed organisations, according to their drug type. Radical drug development still has a lower likelihood of achieving success in all subsamples. The relationship between network density and success rate follows an inverted U-shape in biomedical and mixed organisations, but this is not significant in chemical organisations. One possible reason is that the chemical drugs have well-defined structures and their pharmacology (or that of similar compounds of chemical drugs) has been extensively documented, meaning chemical organisations rely less on external knowledge to ensure efficiency and safety in the process of drug development. In contrast, biomedicines use living material with complex structures that are highly sensitive to every minor change in the manufacturing process; thus, it is important to utilise external knowledge and resources to decrease risks in biomedicine development for biomedical and mixed organisations. Network density still plays a positive moderating role in the relationship between success rate and radicalness.

3.6.2 Implications for theory and practice

The main contribution of this research is to broaden the understanding of the role of research co-operation networks in drug development processes. Co-operation networks are a very important means of acquiring, absorbing and exploiting external knowledge and resources; however, they also require significant effort to coordinate members, so it is important to understand which kind of external knowledge and resources are needed. Drug development was classified into radical and incremental and the moderating role of network density on the relationship between radicalness and success of drug development was explored. This research contributes to the ongoing debate on the performance implications of co-operation network structures (e.g., Rake et al., 2017).

Methodologically, the study offers a new approach that overcomes the huge computational effort to

empirically test the links between radicalness, network density and success rate. It provides a method to measure the radicalness of organisations by clinical trials data. It also builds an indicator to value the approved success rate of organisations according to Danzon et al. (2005).

The research provides organisations and policy-makers with recommendations on the selection between radical and incremental drug development and on how to exploit external knowledge to increase the success rate, in terms of drug approval by legal authorities. It suggests that the selection of radical or incremental drug development is dependent on the capability of acquiring external knowledge. In a dense network, organisations find it easier to acquire external knowledge and increase the success rate of radical drug development. However, for incremental drug development, organisations should focus on exploiting their own knowledge and resources instead of wasting their efforts on promoting member co-operation and increasing network density.

3.6.3 Limitations and future research

Nevertheless, the present study does have some limitations. First, only data from the U.S. Clinical Trials Registry was used. However, as the majority of organisations apply for clinical trials in their own countries first, some clinical trials registered in other countries are overlooked. Although caution should be exercised before generalising the results to the whole world, it is believed that the core mechanisms will work well in the other countries as the processes of drug development are similar. Second, it is postulated that the differences in success rates between radical and incremental drug development are influenced by acquiring external knowledge capability. A detailed study will be necessary in future research to consider the effect of different types of knowledge on the success of drug development; e.g., horizontal and vertical knowledge (Haeussler & Assmus, 2021). A promising avenue of future research will be to combine clinical trials and

other information, including publications and patents, to explore the workflow of drug development. Third, we suggest to build panel data to discuss endogeneity in future research. Fourth, it will be interesting present the dynamic changes of cooperation network and detect the effects of dynamic network on the success of drug development with panel data in future research.

Chapter 4

Applied research to develop cancer drugs, basic research to succeed

4.1 Introduction

Turning scientific research into innovation is a considerable challenge in the medical field (O'Connell & Roblin). Current developments in scientific research have not been mirrored by the same level of progress in drug development (Pammolli et al., 2011), especially with regard to cancer diseases, the most dangerous type of non-communicable disease (World Health Organisation, 2017). Even though research on genetic alterations in human cancers has led to a better understanding of molecular drivers of cancer diseases, and this knowledge should provide more useful drugs, the effectiveness and success rate of cancer drug developments are remarkably low (Hutchinson & Kirk, 2011; Begley & Ellis, 2012). Previous investigations have also confirmed that most medical research organisations focus on publishing novel scientific research instead of developing new drugs (Venditto & Szoka, 2013). This state of affairs is the motivation for the present research to explore the knowledge transfer from scientific research to drug development in cancer diseases.

In academia and industry, all parties support the idea that new drug developments rely on the improvement of scientific research. However, how scientific research can be transferred into drug development is still being discussed. Some scholars support that scientific organisations should participate in drug development directly, as their scientific research helps them better understand pre-clinical results and match the patient conditions with in vitro tests (Van Dongen et al., 2017; Haeussler & Assmus, 2021). However, others believe publishing scientific research and developing drugs both require a great deal of effort, and that organisations do not have enough resources to cover both areas well (Du et al., 2021). Thus, this investigation will explore to what degree the basicness and the scientific impact of research influence organisations to engage in drug development and their effect on its success.

Increasing specialisation and complexities in scientific research widen the knowledge gaps between basic and applied research. In the medical field, basic scientific research is research related to animal experiments; cell studies; biochemical, genetic and physiological investigations; and studies on the properties of drugs and materials. Applied research focuses on both interventional (or experimental) studies and non-interventional (or observational) studies (Röhrig et al., 2009). The first concrete objective of this study is to analyse the effects of the basicness of scientific research on the engagement and success of drug development.

The contribution and quality of scientific research are reflected by the scientific impact of research (Lawani & Bayer, 1983). High-impact research is invariably published through many sources and cited by a large number of adherents; thus, it may guide subsequent trends in scientific research (Aksnes, 2006). The scientific impact of research is also widely used as a standard to evaluate the scientific quality of organisations. In light of this, the second concrete objective of this study is to analyse the effects of the scientific impact of research on the engagement and success of drug development.

Given the limitations of knowledge and resources, some organisations prefer to co-operate with others to develop drugs jointly rather than in isolation (Bignami & Mattsson, 2019). Knowledge spillovers can be generated via co-operation activities (Wang et al., 2017; Hájek & Stejskal, 2018; De Noni et al., 2018). According to Smith (1994), the definition of knowledge spillover is the process of knowledge transfers from producers (knowledge sources) to users (knowledge receivers) through sharing, interaction, and the exchange of knowledge. In a co-operation network, knowledge spillover is always produced as a phenomenon in which the existing research efforts of co-operators may allow a given organisation to achieve results involving less research effort on their part than they would otherwise require (Jaffe, 1986). For

example, in the process of immunological drug development to cure cancer diseases, it is necessary to equip the organisations with knowledge of oncology and immunotherapy. Let us imagine two organisations, A and B, which excel at oncology and immunotherapy, respectively, and which co-operate to develop an immunological drug. It is not necessary for them to have extensive knowledge of both areas, as they can acquire knowledge from their co-operator to fill their knowledge gap with less effort. Through co-operative relationships, the knowledge of oncology (immunotherapy) spills over from organisation A (B) to organisation B (A). In this paper, research co-operation networks are built to observe and analyse the knowledge spillover through co-operative relationships. However, the efficiency of knowledge spillover is different with regard to basic and to applied knowledge, and it is still not clear whether the scientific impact of research can effectively spill over through the co-operation network. Thus, the third objective of this paper is to explore the spillover effects of basicness and the scientific impact of research on the success of drug development in the co-operation network.

To clearly present the research and its contribution, the subsequent parts are organised as follows: Section 4.2 introduces related work and develops research hypotheses; Section 4.3 describes the data collection process and how the variables are measured; Section 4.4 introduces the selected spatial Durbin model and reports on the results of spatial autocorrelation analysis; Section 4.5 provides the main results and validates the robustness of the findings; Section 4.6 presents the conclusions and discusses future areas of work.

4.2 Literature review and hypotheses

In this section, an analysis is made of the effect of basicness and the scientific impact of research on drug development. The direct effect and spillover effect of scientific research are considered and two stages

of drug development are classified; namely, engagement of drug development and success of drug development. Figure 4.1 presents the framework and hypotheses.

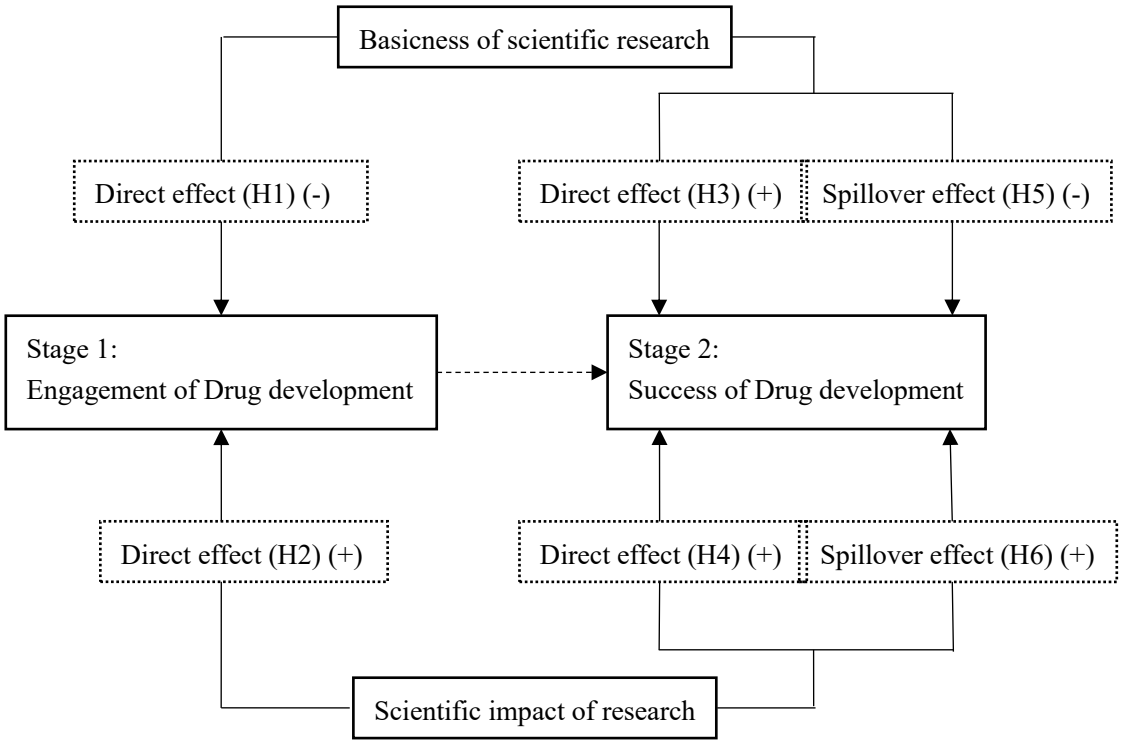


Figure 4.1 The research framework and hypotheses

4.2.1 Basicness of scientific research

Scientific research is classified into basic research and applied research (Narin, 1976; Lewison & Paraje 2004). Basic research is defined as scientific research which aims to better understand and predict natural or other phenomena by improving scientific theories (Partha & David, 1994; NSF, 2009). Basic research focuses on abstract knowledge to explain observed phenomena by creating and either refuting or supporting theories, instead of practical application (Rosenberg& Nelson, 1994). Although basic research is not immediately utilised in commercial applications, it is the basis for promoting progress and development in various fields (NSF, 2009). In contrast, applied research refers to scientific research that uses scientific

methods and knowledge to solve practical problems (Bunge, 1996). Applied research usually has specific commercial objectives related to products, procedures, or services (NSF, 2009).

Drug development always follows a standardised workflow from basic to applied (Willmann et al. 2008), which is also commonly known as “from bench to bedside” (e.g., Mignani et al., 2018; Firestein, 2010). The role of basic research and applied research on drug development is the subject of a long-standing debate: some researchers argue that basic research is necessary to understand the basic principles of drug development (Welch et al., 2019); others uphold that applied research determines the efficiency and quality of drug development (Powell & Gobburu, 2007); whereas a third group of researchers claim that combining basic research with applied research is the key to drug development (Haeussler & Assmus, 2021).

4.2.2 Scientific impact of research

The scientific impact of research reflects the value and quality of scientific research (Wallin, 2005). Scientific research with a high impact always combines important discoveries and essential contributions (Aksnes, 2006) which will guide subsequent research through new methods and theories. In the drug development process, some issues cannot be solved by traditional means, but these new methods and theories of scientific research provide new solutions. Some researchers also support that high-impact research leads to the success of drug development (Magazzini et al., 2012). However, research with a low impact does not mean low scientific quality; it just means this research is not mainstream and is habitually ignored in the scientific field (Arnesen et al., 2020). Some low-impact research requires a long period to achieve an impact (van Raan, 2021) which is a common phenomenon in the medical field (e.g., Ke, 2018; Haghani & Varamini, 2021).

4.2.3 Drug development workflow: engagement and success

Drug development follows a standardised workflow, as presented in Figure 4.2 (Willmann et al., 2008). There are three stages in drug development, including pre-clinical R&D, clinical drug development and launching to market. In pre-clinical R&D, most medical research organisations publish seminal papers on the basic science necessary for the development of a specific drug. In clinical drug development, some organisations test the efficiency and safety of a specific drug in vivo (Venditto & Szoka, 2013). This study considers the engagement of drug development to be the beginning of clinical drug development. In the engagement of drug development, organisations have already selected the target of disease, found promising compounds, and verified the non-toxicity of compounds on animals. The organisations begin to test the safety and efficiency of promising compounds in vivo with healthy people and patients through three phases of clinical trials; subsequently, they engage in drug development.

There are two types of success in drug development: “Phase success” and “success of approval” (Hay et al., 2014). “Phase success” means that the candidate compound achieves good results in a phase of clinical trials. “Success of approval” means that the candidate compound achieves good results from the phase I to phase III clinical trials and is approved by a national authority (notably, the U.S. Food and Drug Administration, FDA). This investigation mainly focuses on the final success of drug development: “success of approval”. Once the drug has been successfully approved, the drug developers always undertake phase IV clinical trials to gather information on the side effects of the drug with several thousand patients.

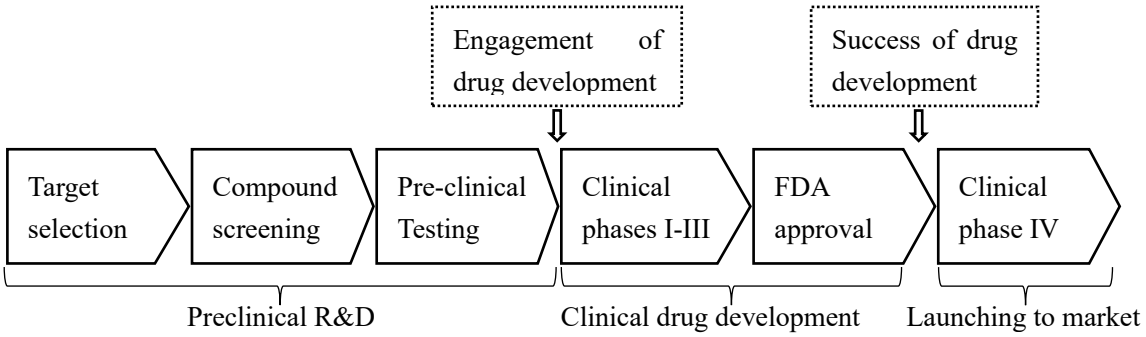


Figure 4.2 The drug development workflow, adapted from Willmann et al. (2008)

4.2.4 The direct effect of the basicness and the scientific impact of research on engagement in drug development

In the engagement of drug development, the main task is to seek appropriate methods to design clinical trials. The organisation requires a perfect protocol to provide and supervise the provision of the experimental drug to patients and to observe its efficacy, any side effects, and patients' reactions (Sullivan, 2004). In a phase I clinical trial of an anti-cancer agent, the participants are all patients and have always exhausted all standard therapeutic options; therefore, it is necessary to design a clinical trial according to the patients' conditions in order to ensure the safety of the experimental drug (Rosa et al., 2006).

Organisations with low basicness focus on the effects of prophylactic intervention, diagnostic procedures and treatment, which is helpful to adjust the clinical trial protocol in order for it to satisfy its purposes. Thus, the organisation with lower basicness of scientific research has more opportunities to design a suitable clinical trial and engage in drug development. On the basis of this, the first hypothesis is formulated:

Hypothesis 1. The basicness of scientific research will decrease the probability of engagement in drug development.

The new methods and theories on the scientific impact of research could spark new ideas to solve problems in the protocol of clinical trials. For example, nano-carriers provide a new means of administration to deliver anti-cancer drugs and circumvent the problems associated with conventional anti-tumour drug delivery systems, including their non-specificity, severe side effects, burst release, and damage to healthy cells (ud Din et al., 2007). An organisation with high-impact research can resolve this dilemma and make up for the defects in engagement in drug development. In light of this, the second hypothesis is formulated:

Hypothesis 2. The scientific impact of research will increase the probability of engagement in drug development.

4.2.5 The direct effect of the basicness and the scientific impact of research on success in drug development

In the process of drug development, organisations need to adjust protocols to increase the efficiency and safety of drug development (Seymour et al., 2010). In the process of clinical trials, organisations with low basicness always react to patients' conditions quickly and provide appropriate medical equipment to maintain the patients' survival. However, they do not have enough knowledge to make a reasonable judgement on the process of a disease with the tested compounds through clinical trials, especially in the case of novel compounds. This causes them to abandon some promising compounds at the beginning of clinical trials. For example, in treatments with immunological antineoplastic agents, patients always worsen at first but will then improve over a longer period of treatment. Organisations with low basicness are more inclined to abandon this kind of drug development when they achieve poor results in the initial stages.

Knowing that high basicness is helpful in analysing anomalies and revising clinical trials according to

patients' reactions instead of abandoning clinical trials, and basic science provides organisations with the skills to examine the causes and investigate the underlying mechanisms. Returning to the case with immunological antineoplastic agents, organisations with high basicness will have already predicted that patients will worsen at the beginning of clinical trials. Thus, they will continue the test for a longer period to investigate the patients' reactions. In addition, organisations with high basicness are better acquainted with aspects of the scientific background of a new drug, including pharmacology, pharmacodynamics, and pharmacokinetics, and are thus better at assessing the chances of a trial being successful and selecting the promising drugs to develop clinical trials. On this basis, the third hypothesis is formulated:

Hypothesis 3. The basicness of scientific research will increase the success of drug development.

Organisations with high-impact research always have novel knowledge (Aksnes, 2006), and they can successfully exploit this frontier knowledge to guide clinical trials. Drug development habitually fails due to unprecedented problems, but high-impact research provides new methods to solve these problems. In addition, organisations with high-impact research are always equipped well with high-level knowledge and useful practical experience (Lawani & Bayer, 1983; Wallin, 2005), which reduces mistakes in the process of drug development. In view of this, the fourth hypothesis is formulated:

Hypothesis 4. The scientific impact of research will increase the success of drug development.

4.2.6 The spillover effect of the basicness and the scientific impact of research on success in drug development

In drug development processing, some organisations prefer to co-operate with others to increase their

success rate (Rake et al., 2021); thus, building the right co-operation network is also a key to achieving success (Ramlogan & Consoli, 2014). Although high basicness is helpful in reducing the risks of drug development, it is difficult to spread abstract basic knowledge in a co-operation network (Du et al., 2019), especially in a fragmented drug development co-operation network. In contrast, applied science provides methods to solve practical problems which are easier to exploit in a co-operation network for drug development (Cassiman et al., 2018). Organisations with low basicness are also well-equipped with clinical experience, which is helpful in order to react to patients' feedback rapidly. Thus, compared with basic science, it is more efficient to transfer applied science and increase the success rate in the co-operation network. In this regard, the next hypothesis is formulated:

Hypothesis 5. The basicness of co-operators' research spillovers will play a negative effect on the success of drug development.

In the drug development process, organisations frequently encounter a number of problems, such as unforeseen side effects. Co-operation with high-impact organisations provides them with an external source to solve these problems, as high-impact organisations are equipped with novel knowledge, which provides new ways to deal with untraditional issues. In addition, co-operation with high-impact organisations is an effective way to learn, acquire, and exploit novel and frontier knowledge. The high-impact research of co-operators will also help organisations design optimal clinical protocols and solve similar problems in the future. On this basis, the next hypothesis is formulated:

Hypothesis 6. The co-operators' high-impact research spillovers will play a positive effect on the success of drug development.

4.3 Model, data and methodology

4.3.1 Data sources

Since cancer diseases are very dangerous and the efficiency and success rate of cancer drug development are remarkably low, it was decided to choose two typical cancer drugs for the sample: alkylating and immunological cancer drugs. Alkylating antineoplastic agents are one of the earliest anti-cancer agents, with a history of more than sixty years. Alkylating antineoplastic agents keep the cell from reproducing (making copies of itself) by damaging its DNA; thus, they destroy cancer cells and healthy cells at the same time. These drugs work in all phases of the cell cycle and are used to treat many different cancers, including cancers of the lung, breast, and ovary as well as leukaemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma (Singh et al., 2018). Immunological antineoplastic agents have advanced in recent years with the development of cancer immunotherapy. Immunological antineoplastic agents deliver and release their cytotoxic drugs to inhibit or prevent the proliferation of cancer cells at the tumour site via the targets, thereby conceptually improving efficacy and reducing toxicity. Immunological antineoplastic agents are targeted agents, and each agent only works on its target; thus, only a few cancer diseases are cured by immunological antineoplastic at present (Chau et al., 2019). Variables were built with reference to the process of drug development through information from publications, clinical trials and FDA-approved drug products in oncology. Publications data was collected from PubMed, since it is the optimal publications database in the biomedical field (Falagas et al., 2007). The U.S. Clinical Trials Registry was chosen due to its greater number of records vis-à-vis other administrations (331,536 in 2019; compared, for instance, with 36,638 clinical trial records in the EU Registry; 29,688 in the Chinese Registry; and 44,051 in the Japanese Registry). Data was collected from several sources:

- **NLM Drug Information Portal**, which provides a gateway to gather drug information from the U.S. National Library of Medicine and other key U.S. Government agencies, including clinical trials (ClinicalTrials.gov) and references from scientific journals (PubMed).
- **ClinicalTrials.gov**, a database maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH), which publishes studies of the U.S. Clinical Trials Registry in all fifty states in the U.S. and in 210 countries, to collect clinical trials data.
- **PubMed**, a resource supporting the search and retrieval of literature in the biomedicine and health fields, along with related disciplines such as life sciences, behavioural sciences, chemical sciences, and bioengineering.
- **Web of Science**, a platform consisting of the information of literature from several literature search databases, including organisations, country, etc.
- **Drugs@FDA**, a database with information about most of the drug products approved since 1939, including organisation name, compounds, indications, etc.
- **iCite**, a web application providing bibliometric information for scientific publications, including scientific impact of research, translation, and citation.

The NLM Drug Information Portal classifies drugs by therapeutic class, so the list of alkylating and immunological cancer drugs was obtained by using the "Antineoplastic Agents, Alkylating" and "Antineoplastic Agents, Immunological" categories, respectively. In the lists, there were 59 alkylating cancer drugs and 45 immunological cancer drugs. Publications were collected from PubMed and clinical trials from ClinicalTrials.gov, respectively, according to the lists. The final database contains 104 drugs, with 250,257 publications and 14,345 clinical trials.

4.3.2 Building the sample and sub-samples

Since 2005, clinical trials have been required to be registered on ClinicalTrials.gov by the International Committee of Medical Journal Editors before the results are published. For the purposes of this study, only the clinical trials from 2005 to 2018 were considered. Given that it takes a few years to apply scientific research into clinical trials, publications were collected from 1996 to 2018.

On ClinicalTrials.gov, organisation names were extracted from the "Sponsor/Collaborators" field. As some publications only show the affiliations of the first authors, affiliation information was collected from the Web of Science for each publication according to PMID. The organisation names of publications were extracted from the affiliations. Clinical trials and publications were matched by organisation name. To improve the matching rate of data between Web of Science and ClinicalTrials.gov, organisation names were normalised by removing individuals' names, cleaning strings with geographic information, and resolving synonymy. After matching, there were 29,723 organisations with publications, of whom 832 had develop clinical trials in alkylating cancer drugs and (or) immunological cancer drugs.

The co-operation networks were built according to the records of "Sponsor/Collaborators" in ClinicalTrials.gov. If Organisation A has co-operated in at least one clinical trial with Organisation B, there is a co-operative relationship between them. There are 591 organisations in clinical trials co-operation networks.

4.3.3 Variables

There are two dependent variables, *Engagement of drug development* and *Success of drug development*. For a given publishing organisation, *Engagement of drug development* means the organisations decide to

develop clinical trials. This takes a value of 1 if that organisation develops clinical trials, and 0 otherwise.

The second dependent variable is *Success of drug development*. It is considered that an organisation achieves success in a given drug development if the FDA approves the corresponding clinical trial on Drugs@FDA, in the case of drug companies, or if it enters into Phase IV on ClinicalTrials.gov (indicating that the drug is on the market), in the case of other organisations (Willmann et al., 2008). For a given publishing organisation with at least one clinical trial, *Success of Drug Development* is the number of successful drugs.

The first independent variable is *Basicness*. This is calculated according to the Triangle of Biomedicine, which maps PubMed papers onto a graph to determine the basicness of the organisations' scientific research (Weber, 2013). Weber (2013) classifies papers into four categories: animals (A), cells and molecules (C), humans (H), and others (O); and maps A-C-H-O categories onto Narin's basic-clinical classification scheme to obtain the scores for each category, as presented in Table 4.1. Each publication is classified into A-C-H-O categories according to Medical Subject Headings (MeSH), which is provided by PubMed; thus, the basic score of each publication is calculated according to its A-C-H-O categories. The basicness of a given organisation is measured by the average of the basic scores of their publications. A higher score means it is more basic.

Table 4.1 The basic scores of A-C-H-O categories (Weber, 2013).

Category	Basic score
A	0.634
C	0.911
H	0.125
O	0.494

For a given organisation, *Basicness* is the average basic score of publications as follows:

$$Basicness_i = \frac{\sum_{i=1}^{N_i}(A_{iq} * 0.634 + C_{iq} * 0.911 + H_{iq} * 0.125 + O_{iq} * 0.494)}{N_i} \quad (1)$$

where $Basicness_i$ is the basicness of organisation i; A_{iq}, C_{iq}, H_{iq} and O_{iq} are the percentages of MeSH topics in each category for organisation i's publication q; and N_i is the number of organisation i's publications.

The second independent variable is *Impact*. The scientific impact of research is calculated according to the Relative Citation Ratio (RCR). RCR quantifies the scientific impact of a research article by its co-citation network to field-normalise the number of citations it has received (Hutchins et al., 2016). The RCR of each article on PubMed can be freely obtained from the iCite website (https://icite.od.nih.gov/analysis) hosted by the NIH. Thus, the *Impact* is expressed as:

$$Impact_i = ln\left(\frac{\sum_{i=1}^{N_i} RCR_{iq}}{N_i}\right) \quad (2)$$

where $Impact_i$ is the scientific impact of organisation i; and RCR_{iq} is the RCR of organisation i's publication q.

Other factors which influence the engagement and success of drug development are monitored: *Publications* are used to reflect the number of scientific research articles; *Organisation Type* to reflect the types of organisations; *Country* to reflect the location of organisations; *Drug, Clinical Trials, Participants* and *Biomedical Percent* to reflect the factors of clinical trials; *Degree Centrality* and *Betweenness Centrality* to reflect the characteristics of co-operation network; and *NIH, Other U.S. Fed, Industry* and *Other Funding*

to reflect the funding sources of organisations in clinical trials development. All the control variables and their measurements are presented in Table 4.2.

Table 4.2 The measurements of variables

variables	Measurement
Engagement of drug development	Whether clinical trials are developed by the given organisation.
Success of drug development	The number of successful drugs for the given organisation.
Basicness	The basicness of scientific research for the given organisation.
Impact	The scientific impact of research for the given organisation.
Publication	$Publication_i = ln(Number\ of\ publications_i)$, where $Number\ of\ publications_i$ is the number of publications of organisation i.
Organisation type	Organisation type is a set of dummy variables containing four types of organisation, including Company, Hospital, Higher education, Research centre, and Other organisation.
Country	*Country* is a set of dummy variables of the top ten countries in the number of publications and other organisations. The top ten countries sorted by the number of publications are the USA, China, Italy, Germany, France, Japan, the UK, Spain, India, and Australia.
Drug	$Drug_i = ln(Number\ of\ drugs_i)$, where $Number\ of\ drugs_i$ is the number of drugs of organisation i.
Clinical trials	$Clinical\ trials_i = ln\left(\frac{Number\ of\ Clinical\ trials_i}{Number\ of\ Drugs_i}\right)$, where $Number\ of\ Clinical\ Trials_i$ is the number of clinical trials of organisation i.
Participants	$Participants_i = ln\left(\frac{Number\ of\ participants_i}{Number\ of\ drugs_i}\right)$, where $Number\ of\ participants_i$ is the number of participants of organisation i.
Biomedical percent	$Biomedical\ Percent_i = ln\left(\frac{Number\ of\ Immunological\ drugs_i}{Number\ of\ drugs_i}\right)$, where $Number\ of\ Immunological\ Drugs_i$ is the number of immunological drugs of organisation i.
Degree centrality	$Degree\ centrality_i = \frac{\sum_{j=1}^{n}\rho_{ij}}{g-1}\ (i \neq j)$, where ρ_{ij} is the co-operative relationship between organisation *i* and organisation *j, n* is the number of organisations in the co-operation network.
Betweenness centrality	$Betweenness\ Centrality_i = \sum_{s\neq i\neq j}\frac{\sigma_{sji}}{\sigma_{sj}}$, where σ_{sj} is the total number of shortest paths from organisation *s* to organisation *j*, σ_{sji} is the number of those paths that pass through organisation *i*.
NIH	The percentage of clinical trials which were funded by the U.S. National Institutes of Health for the given organisation.
Other U.S. Fed	The percentage of clinical trials which were funded by Other U.S. Fed (including Food and Drug Administration, Centers for Disease Control and Prevention, or U.S. Department of Veterans Affairs) for the given organisation.
Industry	The percentage of clinical trials which were funded by pharmaceutical and device companies for the given organisation.
Other Funding	The percentage of clinical trials which were funded by Other Sources (including individuals, universities and community-based organisations) for the given organisation.

4.4 Descriptive statistics

This study investigates the effects of basicness and scientific impact on the engagement and success of drug development. This section mainly describes the distribution of key variables and sample.

4.4.1 Descriptive statistics by organisation type

Table 4.3 shows the number and percentage of organisations with publications. There are 26,833 organisations with publications but only a few of them engage in clinical trials (3.1%). Hospitals participate actively both in publications (54%) and clinical trials (38%). Companies tend to develop clinical trials (28%) rather than papers (11%). The percentages of higher education, public research and other organisations are low both in publications and clinical trials. One possible reason for hospitals to publish unusually more than higher education and public research organisations is that this study only focuses on cancer drugs-related publications. Hospitals pay more attention to drug development and develop more drug-related publications than higher education and public research organisations, which is in line with the results of Lou et al. (2020).

Table 4.3 The number and percentage of organisations with publications and clinical trials

	Number of organisations with publications	**Percentage of organisations with publications**	**Number of organisations with clinical trials**	**Percentage of organisations with clinical trials**
Company	3,026	11%	231	28%
Hospital	14,523	54%	316	38%
Higher education	4,185	16%	154	19%
Public research organisation	3,359	13%	101	12%
Other organisation	1,740	6%	30	4%
Total	26,833	100%	832	100%

Figure 4.3 displays the percentage of organisations engaged into drug development by organisation type. Companies (7.63%) are the most active organisation type. Although many hospitals engage in drug development (see table 4.3, 38% of hospitals with clinical trials), the percentage of engaged hospital is low (3.68%).

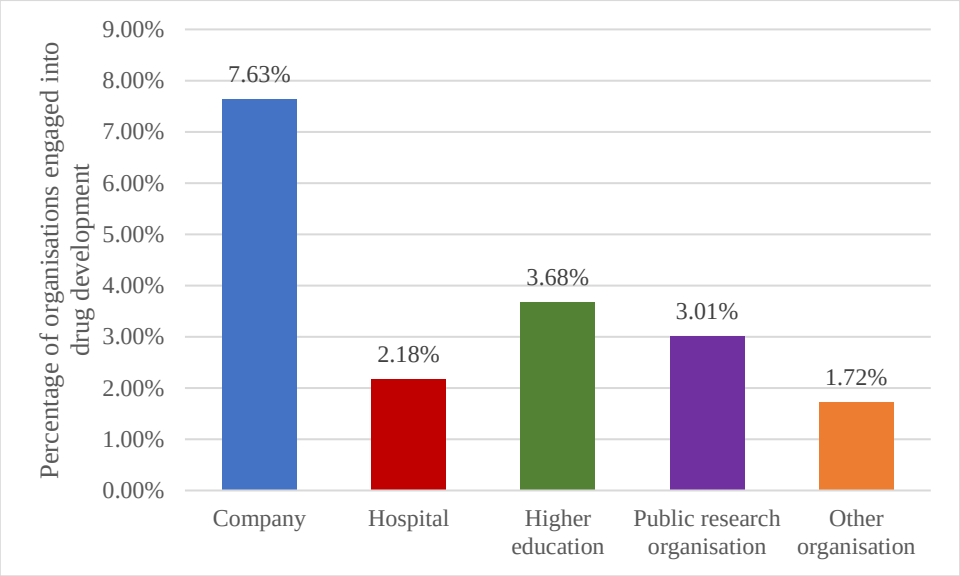


Figure 4.3 Percentage of organisations engaged into drug development by organisation type

Figure 4.4 shows the average number of publications by type of organisation. Compared with Table 4.3, although only 16% of organisations with publications belong to the higher education sector, the average number of publications in higher education is much higher (39.21) than the other types of organisations. In line with common sense, higher education mainly focuses on developing scientific research, such as publications. Many hospitals have publications, but the average number of publications per hospital is not very high (11.41). Companies have the lowest number of average publications, which means companies tend to keep secrecy.

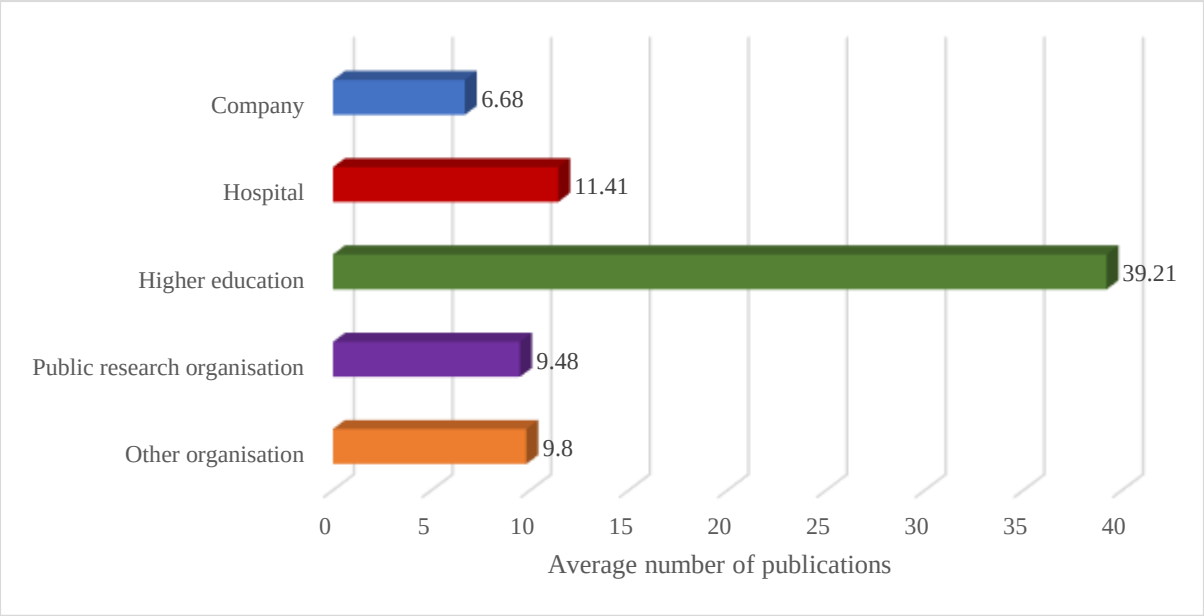


Figure 4.4 Average number of publications by type of organisation

4.4.2 Descriptive statistics of key variables

Table 4.4 presents the results of the descriptive statistics of the variables of the full sample, the sample that engages in drug development, and the sample that co-operate to develop drugs. In the full sample, only 2.8% of organisations develop drugs. The average values of *Basicness* are almost the same in the full and sub-samples. The average value of *Impact* is higher in the sub-sample with drug development (1.081) than the full sample (0.842), which means the organisations with high-impact research are more inclined to develop drugs. The average value of *Publication* is highest in the sample with co-operation networks (3.364) than in the sample with drug developments (2.956) and the full sample (0.842), which means the organisations with drug development always have more scientific research, especially those organisations in drug co-operation networks. Comparing the sectors of organisations, hospitals are very active in scientific research, drug development and co-operation. Companies are more focused on drug development than

scientific research. The success rate of drug development is higher in co-operative organisations than the others. In the co-operation networks, organisations develop more drugs with fewer clinical trials and with more participants than the others. The funding sources of co-operative organisations are similar to those of the others.

Table 4.4 Descriptive statistics of the variables

	Full sample (N=26833)				Sample with drug development (N=832)				Sample with co-operation network (N=591)			
Variables	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**	**Mean**	**Std. Dev.**	**Min**	**Max**
Engagement of drug development	0.028	0.165	0.000	1.000								
Success of drug development					0.267	0.753	0.000	8.000	0.332	0.849	0.000	8.000
Basicness	0.451	0.535	0.255	0.709	0.460	0.038	0.306	0.660	0.458	0.036	0.310	0.637
Impact	0.835	0.659	0.000	5.572	1.081	0.639	0.000	4.869	1.110	0.609	0.000	4.278
Publication	0.842	1.301	0.000	9.270	2.956	2.186	0.000	9.185	3.364	2.045	0.000	9.185
Company	0.112	0.316	0.000	1.000	0.275	0.447	0.000	1.000	0.235	0.424	0.000	1.000
Hospital	0.541	0.498	0.000	1.000	0.382	0.486	0.000	1.000	0.406	0.492	0.000	1.000
Higher education	0.156	0.362	0.000	1.000	0.189	0.392	0.000	1.000	0.190	0.392	0.000	1.000
Public research organisation	0.125	0.331	0.000	1.000	0.120	0.326	0.000	1.000	0.130	0.337	0.000	1.000
Other organisation	0.065	0.246	0.000	1.000	0.033	0.180	0.000	1.000	0.039	0.194	0.000	1.000
Number of drugs					0.894	0.987	0.000	3.784	1.101	0.919	0.693	3.784
Ratio of clinical trials					0.945	0.693	0.000	4.043	0.473	0.597	0.000	4.025
Participants					4.778	1.431	0.000	10.284	4.920	1.435	0.000	9.346
Biomedical					0.599	0.376	0.000	1.000	0.583	0.348	0.000	1.000
Degree centrality									0.005	0.008	0.000	0.113
Betweenness centrality									0.114	0.638	0.000	11.9
NIH					0.023	0.085	0.000	1.000	0.031	0.098	0.000	0.600
Other U.S. Fed					0.004	0.047	0.000	1.000	0.005	0.046	0.000	0.500
Industry					0.261	0.317	0.000	1.000	0.235	0.260	0.000	1.000
Other sources					0.711	0.323	0.000	1.000	0.728	0.273	0.000	1.000

To examine the difference between the two independent variables - *Basicness* and *Impact* - in more depth, Table 4.5 shows their cross-distribution. The mean values were set for *Basicness* (0.451) and *Impact* (0.835) as thresholds. Most organisations (31.66%) have low basicness and impact. The percentage of high basicness and low impact organisations is similar to that of low basicness and high impact organisations (slightly over a quarter). A few organisations have high basicness and are high-impact organisations.

Table 4.5 The cross-distribution of *Basicness* and *Impact*

	Low basicness	**High basicness**
Low impact	8,494 (31.66%)	7,017 (26.15%)
High impact	7,395 (27.56%)	3,927 (14.63%)

Figure 4.5 displays the average basicness of each type of organisation. The solid bars show the average basicness of organisations with publications (with or without clinical trials), and the dotted bars show the average basicness of organisations with publications and clinical trials. The basicness values of all types of organisations are similar (from 0.44 to 0.48). The basicness level of organisations with clinical trials is slightly lower than organisations with publications except for the hospital. One possible reason is that the high basicness of hospitals helps them to understand the medical knowledge which is beneficial for them to conduct clinical trials. Other types of organisations prefer to develop clinical trials with high-basicness hospitals rather than with the low-basicness hospitals.

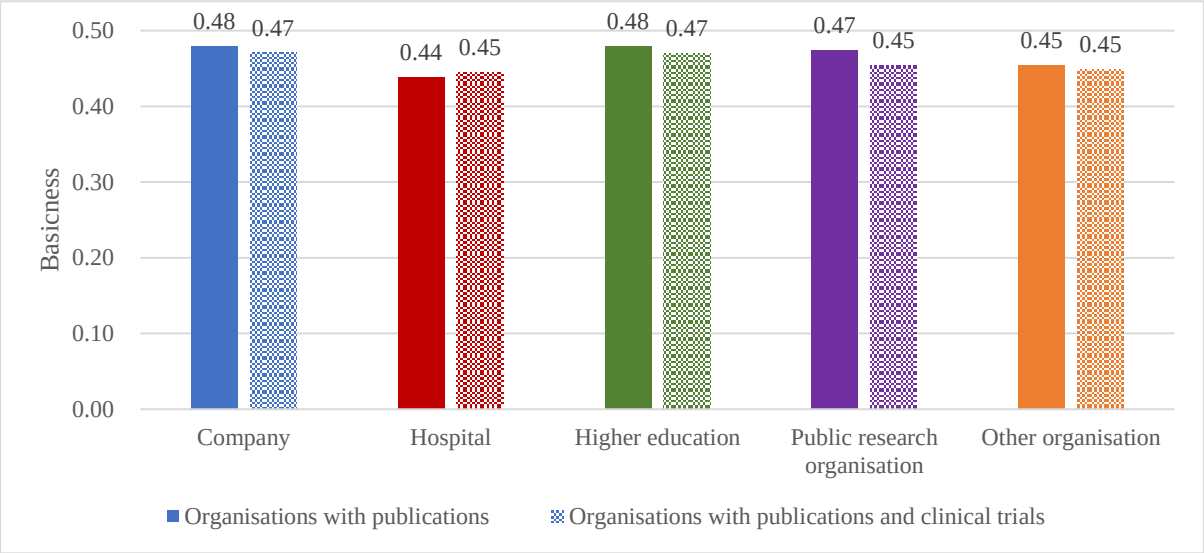


Figure 4.5 Average basicness of organisation with publications and clinical trials

Figure 4.6 displays the scientific impact of each type of organisation. The solid and dotted bars show the organisations with publications and clinical trials respectively. The organisations with clinical trials have higher scientific impact than the others. Compared with Table 4.3, although higher education organisations generate most of the publications, their scientific impact is the lowest. One possible reason is that in drug development, higher scientific impact publications always include more evidence from clinical medicine (Noguchi et al., 2020). Compared with other types of organisations, higher education organisations have less experience in clinical medicine, thus the scientific impact of higher education's publications is lower than the other types of organisations.

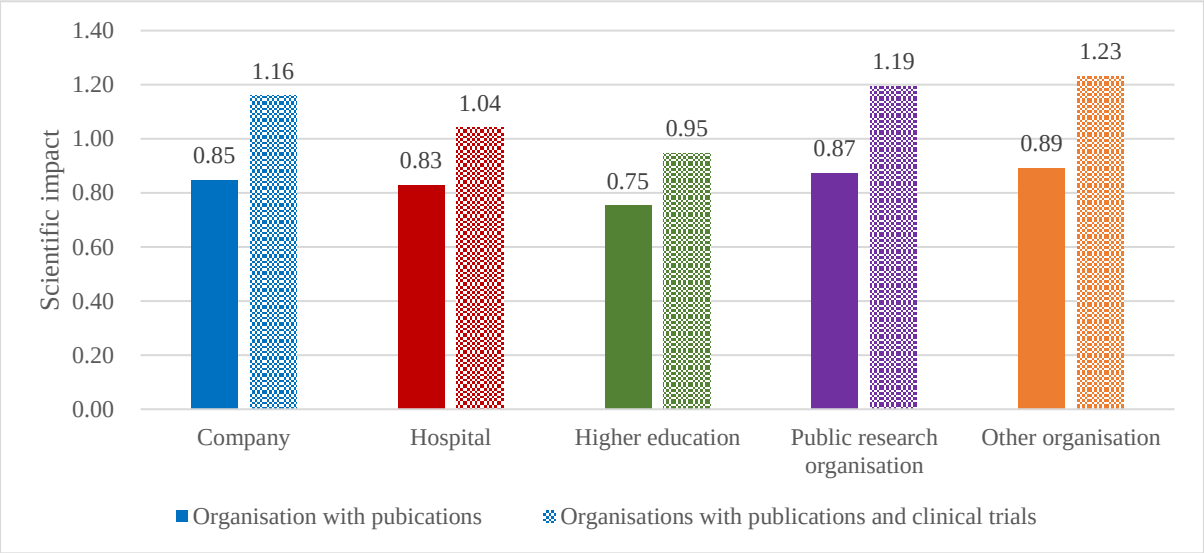


Figure 4.6 Average scientific impact of organisations with publications

4.4.3 Descriptive statistics of Top 10 organisations

Table 4.6 lists the top 10 organisations according to the number of publications on alkylating and immunological antineoplastic agents. The typical top 10 organisation is a *Hospital.* The MD Anderson Cancer Center ranks first, with 10,619 publications. The values of *Basicness* of the top 10 organisations are around the average value of all samples (0.451). The *impact* of the top 10 organisations is much higher than the average value (0.835). Every top 10 organisation engages in cancer drug development; however, the success rate is very low. Since data was collected from the U.S. Clinical Trials Registry, most of the organisations come from the U.S., except Assistance Publique - Hopitaux de Paris, Institut national de la santé et de la recherche médicale, and Gustave Roussy, which are located in France.

Table 4.6 Top 10 organisations in the number of publications of alkylating and immunological antineoplastic agents from 2005 to 2018

Rank	Organisation name	Number of publications	Basicness	Impact	Engagement of drug development	Number of drugs	Number of successful drugs	Success rate	Country	Organisation type
1	MD Anderson Cancer Center	10,619	0.441	3.259	Yes	30	1	0.033	U.S.	Research centre
2	Memorial Sloan Kettering Cancer Center	5,930	0 .437	5.833	Yes	25	0	0.000	U.S.	Hospital
3	National Cancer Institute	4,,439	0. 466	2.807	Yes	44	0	0.000	U.S.	Research centre
4	University of California	3,924	0.461	3.177	Yes	23	1	0.043	U.S.	University
5	Assistance Publique - Hopitaux de Paris	3,771	0.430	2.717	Yes	17	2	0.118	France	Hospital
6	Dana Farber Cancer Institute	3,326	0.439	5.229	Yes	24	0	0.000	U.S.	Hospital
7	Institut national de la santé et de la recherche médicale	3,132	0.459	2.731	Yes	1	0	0.000	France	Research centre
8	Mayo Clinic	2,673	0.439	2.889	Yes	1	18	0.056	U.S.	Hospital
9	Ohio State University	2,585	0.463	2.918	Yes	20	4	0.200	U.S.	University
10	Gustave Roussy	1,820	0.437	4.979	Yes	14	0	0.000	France	Hospital

4.5 Model selection

The unit of observation of this study is a publishing organisation. In this investigation, the direct effect of the basicness and the scientific impact of research on the engagement of drug development is explored first. Considering the first dependent variable, *Engagement of drug development*, is a dummy variable, as only a few publishing organisations are engaged in drug development, this means that only a few values (2.8%) of *Engagement of drug development* are 1. Thus, rare events logistic regression is used to test the direct effect of the basicness and the scientific impact of research on the engagement of drug development. The rare events logistic is used in the case of binary dependent variables with dozens to thousands of times fewer ones than zeros to avoid underestimating the probability of rare events (Toms et al., 2003).

In addition, for publishing organisations engaged in drug development, the direct effect and spillover effect of the basicness and the scientific impact of research on the success of drug development are also analysed. The classical econometric models are usually estimated by the OLS method, neglecting the spatial interaction or spillover effects between study units, which may thus lead to deviations in model estimation results (Elhorst, 2003, LeSage & Pace, 2010). The spatial econometric model is an effective way of solving the problem of bias and inconsistency of estimated coefficients (Anselin, 1988). In order to select a proper spatial econometric model for the study, the spatial weight matrix will be built first according to the co-operation matrix of drug development and the spatial autocorrelation analysis will be conducted, which is the basis for the following model selection, then the selected model and the reasons for its choice will be introduced.

4.5.1 Spatial weights matrix

The spatial weights matrix quantifies the spatial relationships between two spatial units. The common ways to build a spatial weights matrix are through adjacency distance, geographic distance, economic distance, and comprehensive distance, etc. As the spatial autocorrelation and the results of the spatial econometric model directly depend on the spatial weights matrix, it is necessary to select an appropriate conceptualisation to reflect the interactions of each spatial unit. In this paper, the spillover effect in the co-operation network of drug development is explored; therefore, the co-operation matrix is set as a spatial weight matrix. Accordingly, *W* is set as the *N*×*N* vector spatial weight matrix; w_{ij} is the element in the *N*×*N* vector spatial weight matrix (*W*); *i* and *j* denote the organisations ($i \neq j$), if there is at least one co-operation clinical trial between organisation *i* and organisation *j*, $w_{ij} = 1$; otherwise, it is $w_{ij} = 0$.

4.5.2 Spatial autocorrelation analysis

Spatial autocorrelation refers to that the values of the variables are related spatially. The Global Moran's Index (I) test is a typical method to test spatial correlation based on both feature locations and feature values simultaneously (Moran, 1948). The global Moran's I statistic for spatial autocorrelation strength is calculated as:

$$\mathrm{I} = \frac{n\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}\,(x_i - \bar{x})(x_j - \bar{x})}{\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}(x_i - \bar{x})^2} \tag{3}$$

where I denotes the global Moran's I, *n* is the number of organisations in a co-operation network, x_i (or x_j) is the corresponding attribute value of listing *i* (or *j*), and $\bar{x}$ is the average value of x_i. The spatial autocorrelation of dependent variables *Success of Drug Development* is tested. In general, I ranges from -1

to 1. If I is closer to 1 (-1), there is a higher positive (negative) correlation on spatial distribution, and if I=0, independent random distribution exists on spatial distribution. The global Moran's I of *Success of Drug Development* is 0.0329 at the 1% significance levels, which indicates there is a positive spatial autocorrelation of *Success of Drug Development* (Moran, 1948). The spatial autocorrelation result that supports the spatial model should be selected.

4.5.3 Spatial Durbin model

Generally speaking, the spatial econometric models include the spatial lag model (SLM), the spatial error model (SEM), and the spatial Durbin model (SDM). SLM assumes that the dependent variable has a spatial dependence, but is incapable of analysing the influence of explanatory variables in the adjoining areas (Manski, 1993). SEM emphasises the spatially autocorrelated error term and neglects the spatial lag of the explained variable (Manski, 1993). The spatial Durbin model (SDM) can test the influence of the explained variables in the local area as well as explained variables in neighbouring areas (LeSage & Pace, 2010). This study focuses on the direct and spillover effect of the basicness and the scientific impact of research; thus, SDM is much more suitable. Considering that the data of this study is cross-section data, the cross-section spatial Durbin model is used to analyse the effects of the basicness and the scientific impact of research. The following is a general specification for the panel spatial Durbin model.

$$
\begin{aligned}
&Success\ of\ drug\ development_i \\
&= \delta \sum_{j=1}^{n} w_{ij} Success\ of\ drug\ development_j + \alpha + \beta_1 Basicness_i \\
&+ \beta_2 Impact_i + \theta_1 Cooperators'\ basicness\ spillovers_i \\
&+ \theta_2 Cooperators'\ impact\ spillovers_i + u_i + \varepsilon_i
\end{aligned}
\tag{4}
$$

Where δ represents the spatial autocorrelation coefficient; α is the constant term; β_1 and β_2 comprise the coefficients of *Basicness* and *Impact*, respectively; θ_1 and θ_2 represent the spatial coefficient of *Co-operators' basicness spillovers* and *Co-operators' impact spillovers*, respectively; u_i is the region fixed effect; and ε_i is the random error term. The spillover effect of independent variables is tested by $\sum_{j=1}^{n} w_{ij} x_j \theta$. Thus, the basicness spillover of organisation *i*'s co-operators is $Cooperators'basicness\ spillovers_i = \sum_{j=1}^{n} w_{ij} Basicness_j$, and the scientific impact spillover of organisation *i*'s co-operators is $Cooperators'impact\ spillovers_i = \sum_{j=1}^{n} w_{ij} Impact_j$.

4.6 Results and robustness test

This study tests the effects of basicness and scientific impact on the engagement and success of drug development. Table 4.7 and 4.8 display the correlations of variables with the full sample and the sample with co-operation networks. According to Table 4.8, the correlation between variables is low, including between *Basicness* and *Impact*. Additionally, the variance inflation factor (VIF) was applied to test multicollinearity. The VIF scores were calculated for each predictor variable, and all scores were below 2.93, indicating that multicollinearity was not an issue in the model (Neter et al., 1996).

Table 4.7 Correlations of the variables in full samples

Variables	1	2	3	4	5	6	7	8
1. *Engagement of drug development*								
2. *Basicness*	-0.000							
3. *Impact*	**0.065**	**-0.106**						
4. *Publication*	**0.253**	**-0.023**	**0.176**					
5. *Company*	**0.075**	**0.174**	0.008	**-0.077**				
6. *Hospital*	**-0.048**	**-0.350**	-0.005	**-0.043**	**-0.392**			
7. *Higher Education*	**0.017**	**0.204**	**-0.038**	**0.192**	**-0.151**	**-0.445**		
8. *Public research organisation*	-0.005	**0.138**	**0.023**	**-0.030**	**-0.143**	**-0.420**	**-0.162**	
9. *Other organisation*	**-0.019**	0.001	**0.023**	**-0.058**	**-0.099**	**-0.290**	**-0.112**	**-0.106**

Note. The correlation estimates in bold are significant at the 0.05 level.

Table 4.8 Correlations of the variables in sample with co-operation network

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. *Engagement of drug development*																		
2. *Basicness*	**0.056**																	
3. *Impact*	-0.051	**-0.108**																
4. *Publication*	**0.161**	-0.002	**0.109**															
5. *Number of drugs*	**0.238**	-0000	**0.131**	**0.351**														
6. *Ratio of clinical trials*	**0.296**	0.029	**0.168**	**0.286**	**0.611**													
7. *Participants*	**0.257**	0.040	**0.108**	**0.091**	**0.400**	**0.502**												
8. *Biomedical*	**-0.095**	0.006	**0.100**	0.052	**-0.130**	-0.018	-0.012											
9. *Degree centrality*	**0.361**	0.005	0.041	0.336	**0.526**	0.595	0.376	-0.057										
10. *Betweenness centrality*	**0.379**	-0.007	0.048	0.203	**0.305**	**0.467**	0.267	-0.030	0.792									
11. *Company*	0.018	**0.133**	**0.100**	**-0.311**	-0.005	**0.126**	0.097	0.001	-0.022	0.060								
12. *Hospital*	-0.051	**-0.221**	**-0.096**	-0.018	**-0.045**	**-0.160**	-0.118	-0.040	-0.017	-0.072	**-0.458**							
13. *Higher education*	**0.162**	**0.182**	**-0.117**	**0.496**	0.033	-0.015	-0.028	0.058	0.054	-0.006	**-0.268**	**-0.400**						
14. *Public research organisation*	-0.104	-0.005	**0.125**	**-0.106**	0.026	0.075	0.074	-0.011	-0.047	-0.014	**-0.215**	**-0.320**	**-0.187**					
15. *Other organisation*	-0.058	-0.009	0.043	**-0.094**	0.013	0.027	0.014	0.000	0.064	**0.089**	**-0.112**	**-0.166**	**-0.097**	-0.078				
16. *NIH*	-0.005	0.067	**0.158**	**0.089**	**0.222**	**0.240**	0.047	-0.059	0.164	**0.112**	-0.020	**-0.154**	-0.022	**0.212**	**0.111**			
17. *Other U.S. Fed*	-0.033	0.022	**0.043**	**0.090**	-0.080	-0.041	-0.092	0.078	-0.025	-0.012	-0.059	-0.007	0.044	-0.033	**0.116**	0.021		
18. *Industry*	-0.023	0.075	**0.203**	**-0.212**	**0.118**	**0.228**	0.026	0.037	0.001	0.062	**0.619**	**-0.326**	**-0.249**	-0.018	0.008	-0.062	-0.080	
19. *Other sources*	0.047	**-0.099**	**-0.258**	**0.155**	**-0.178**	**-0.297**	-0.026	-0.027	0.055	**-0.111**	**-0.573**	**0.367**	**0.238**	-0.053	-0.067	**-0.302**	**-0.102**	**-0.928**

Note. The correlation estimates in bold are significant at the 0.05 level.

4.6.1 Main results

The results with the full sample are presented first (Table 4.9), then those of the sub-sample with co-operation networks (Table 4.10). In Table 4.9, the direct effect of the basicness and the scientific impact of research on the engagement of drug development is tested. Since the dependent variable, *Engagement of drug development*, is a dummy variable and there are only a few values equal to 1, rare events logistic regression was run in Table 4.9. In Table 4.9, column 1, only the control variables are used. In Table 4.9, column 2, the independent variables *Basicness* and *Impact* are added. The coefficient of *Basicness* is negative and significant in Model 2, which means organisations with more basicness have fewer motivations to develop drugs, supporting ***Hypothesis 1***. The coefficient of *Impact* is positive and significant, which indicates the scientific impact of research encourages organisations to develop drugs, supporting ***Hypothesis 2***.

With regard to the control variables, the coefficients of *Publications* are positive and significant, which reflects that more scientific research stimulates organisations to develop drugs. Comparing the sectors, companies and research centres are more inclined to develop drugs. The reason for this is that companies focus on making new products and launching them on the market to obtain returns, and most medical research centres pay attention to finding new methods to cure patients, which encourages them to explore new treatments in drug development.

Table 4.9 The direct effect of the basicness and the scientific impact of research on the engagement of drug development

	(1)	**(2)**
	Rare events	**Rare events**
Basicness (H1)		-2.845***
		(0.963)
Impact (H2)		0.204***
		(0.067)
Publication	0.758***	0.737***
	(0.022)	(0.023)
Company	1.733***	1.765***
	(0.253)	(0.249)
Hospital	0.278	0.222
	(0.247)	(0.244)
Higher education	-0.252	-0.171
	(0.254)	(0.251)
Public research organisation	0.696***	0.714***
	(0.264)	(0.261)
Country	Control	Control
Constant	-5.028***	-3.896***
	(0.252)	(0.515)
N	26833	26833

*Note. Robust standard errors in parentheses; * p < 0.1, ** p < 0.05, *** p < 0.01. No collinearity according to VIF.*

In Table 4.10, the direct and spillover effects of the basicness and the scientific impact of research on the success of drug development are tested. In Model 3, only the control variables are included. The dependent variable, *Success of drug development*, is the count variable, and the Vuong test favours zero inflated over standard binomial regression (z=5.79, p=0.000). In addition, the AIC and BIC values of zero inflated negative binomial regression (AIC=890.52 and BIC=1018.06) are lower than negative binomial regression (AIC=965.64 and BIC=1027.05). Therefore, zero inflated negative binomial regression is used. In Model 4, two independent variables are added, *Basicness* and *Impact*, and their direct effects are tested

by the zero inflated negative binomial regression. In Model 5, the Spatial Durbin model is used to test the direct and spillover effects of *Basicness* and *Impact*. The *Co-operators' basicness* and *Co-operators' impact spillovers* show the spillover effects of *Basicness* and *Impact*, respectively. In Models 4 and 5, the coefficients of *Basicness* are positive and significant, which means basic science is very useful in drug development, as organisations select more promising drugs and modify the test for better results according to basic research, supporting ***Hypothesis 3***. In Models 4 and 5, the coefficients of *Impact* are positive and significant, which indicates organisations with scientific impact of research are equipped with very good and frontier knowledge to avoid mistakes and find new solutions to develop drugs, supporting ***Hypothesis 4***. In Model 5, the coefficient of *Co-operators' basicness spillovers* is negative and significant, supporting ***Hypothesis 5***. The reason for this is that basic knowledge is too abstract to acquire and absorb in a co-operation network, but applied knowledge is easier to transfer. In Model 5, the coefficient of *Co-operators' impact spillovers* is positive and significant, which means a co-operation network is a good source in which to transfer and exploit research with high scientific impact to increase the success rate, supporting ***Hypothesis 6***.

Table 4.10 The direct and spillover effect of the basicness and the scientific impact of research on the success of drug development

	(3) Zinb	(4) Zinb	(5) SDM
Basicness (H3)		5.723*	3.343*
		(3.441)	(1.733)
Impact (H4)		0.775***	0.268*
		(0.248)	(0.139)
Co-operators' basicness spillovers (H5)			-0.262***
			(0.058)
Co-operators' impact spillovers (H6)			0.040**
			(0.019)
Publication	-0.056	-0.088	-0.126***
	(0.056)	(0.058)	(0.041)
Number of drugs	0.361***	0.299**	0.295***
	(0.125)	(0.127)	(0.089)
Ratio of clinical trials	0.034	0.052	-0.025
	(0.226)	(0.222)	(0.221)
Participants	0.389***	0.395***	-0.004
	(0.102)	(0.101)	(0.049)
Biomedical	-0.415	-0.492*	-0.517***
	(0.270)	(0.275)	(0.186)
Degree centrality			66.934*
			(26.863)
Betweenness centrality			0.503***
			(0.087)
Hospital	0.273	0.245	0.112
	(0.371)	(0.344)	(0.171)
Higher education	0.795*	0.893**	0.443**
	(0.438)	(0.402)	(0.222)
Public research organisation	0.378	0.640	-0.118
	(0.505)	(0.443)	(0.184)
Other organisation	-1.617**	-1.912***	-0.403**
	(0.679)	(0.678)	(0.195)
Other U.S. Fed	-2.239	-2.482	1.086
	(4.869)	(4.788)	(1.163)
Industry	2.067	1.869	0.040
	(1.687)	(1.671)	(0.678)
Other sources	1.996	1.997	0.579
	(1.592)	(1.586)	(0.735)
Constant	-4.632***	-7.830***	-0.082
	(1.759)	(2.349)	(1.215)
R^2			0.114
chi2	83.20	93.17	73.784
P-value	0.000	0.000	0.000
N	832	832	591

*Note. Robust standard errors in parentheses; * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. No collinearity according to VIF.*

With regard to the control variables, the coefficients of *Drug* are positive and significant, which reflects that organisations with the capability to develop more drugs have more opportunities to achieve success, as they always have more knowledge and resources to develop drugs and their previous experience of drug development decreases the risks. The coefficients of *Higher education* are positive and significant, and the coefficients of *Other organisation* are negative and significant, which means universities (other organisations) have more (less) opportunities to achieve success in drug development than companies. One possible reason for this is that universities have more knowledge to deal with issues, and other organisations have less clinical experience and knowledge to solve problems in the drug development process.

4.6.2 Robustness check

In addition to the main analyses, two robustness checks were also conducted. The independent variable of *Basicness* may ignore the differences between the organisations which develop both basic and applied research and the organisations which develop either basic or applied research. The first robustness check (Table 4.11 Models 6–7) uses a set of dummy variables (*Basic only*, *Applied only,* and *Basic and applied*) to classify organisations into types. In this method, the basic score of publications is calculated first, as follows:

$$Basicness_{iq} = A_{iq} ** 0.634 + C_{iq} * 0.911 + H_{iq} * 0.125 + Other_{iq} * 0.494 \quad (6)$$

where $Basicness_{iq}$ is the basic score of organisation i's publication q. If $Basicness_{iq} > 0.5$, the publication q of organisation i is basic research. If $Basicness_{iq} < 0.5$, the publication q of organisation i is applied research. The $Basic\ only_i$ =1 if all publications of organisation i are basic research. The $Applied\ only_i$=1 if all publications of organisation i are applied research. The $Basic\ and\ applied_i$=1 if publications of organisation i include basic research and applied research.

Table 4.11 Model 6 tests the effect on the engagement of drug development. The coefficient of *Basic only* is negative and significant, and the coefficient of *Basic and applied* is positive and significant, which means the basic-only organisations are less likely to participate drug development process, supporting H1. Model 7 tests the direct effect of basicness on the success of drug development. The coefficient of *Basic only* is positive and significant, which means basic-only organisations have more opportunities to achieve success in drug development, supporting H3. Similarly, H4 on the positive effect of *Impact* is also supported. In Model 8, the coefficient of *Co-operators' basic only spillovers* is not significant and the coefficient of *Co-operators' basic and applied spillovers* is negative and significant, which means that, compared with co-operation with applied-only organisations, co-operation with mixed organisations provides less opportunities to achieve success. This result partially supports H5. One possible reason is the organisations which co-operate with pure basic (applied) organisations are well-equipped with knowledge and resources to learn and absorb pure basic (applied) knowledge form the external sources. The productivities and success rate of these organisations are similar. The organisations which co-operate with mixed organisations have to make a great deal of effort and require a long period to adjust and to learn mixed knowledge. They cannot learn and absorb mixed knowledge rapidly and increase their productivity and success rate in the short term.

Table 4.11 The results of robustness check

	(6) Rare events Engagement	(7) Zinb Success	(8) SDM Success	(9) Zinb with sample selection Success	(10) SDM with sample selection Success
Basic only	-0.478***	0.897**	0.206		
	(0.170)	(0.429)	(0.258)		
Basic and applied	0.483***	0.221	-0.065		
	(0.123)	(0.396)	(0.190)		
Basicness				5.405*	3.449**
				(3.162)	(1.727)
Impact	0.236***	0.768***	0.200**	0.773***	0.233
	(0.064)	(0.199)	(0.080)	(0.201)	(0.145)
Co-operators' basic only spillovers			0.172		
			(0.196)		
Co-operators' basic and applied spillovers			-0.105***		
			(0.025)		
Co-operators' basicness spillovers					-0.273***
					(0.061)
Co-operators' impact spillovers			0.039***		0.044**
			(0.015)		(0.020)
Publication	0.710***	-0.105	-0.109**	-0.060	-0.214**
	(0.035)	(0.067)	(0.046)	(0.116)	(0.105)
Number of drugs		0.323***	0.309***	0.302***	0.295***
		(0.105)	(0.089)	(0.104)	(0.090)
Ratio of clinical trials		-0.028	-0.041	0.069	-0.066
		(0.257)	(0.231)	(0.237)	(0.221)
Participants		0.417***	-0.008	0.391***	0.005
		(0.101)	(0.053)	(0.102)	(0.049)
Biomedical		-0.487**	-0.445**	-0.502**	-0.465***
		(0.236)	(0.184)	(0.234)	(0.172)
Degree centrality			29.781		66.640**
			(30.794)		(27.037)
Betweenness centrality			0.521***		0.506***
			(0.102)		(0.087)
Hospital	-1.455***	0.053	0.243	0.174	0.280
	(0.110)	(0.358)	(0.174)	(0.348)	(0.224)
Higher education	-1.983***	0.840**	0.680***	0.819*	0.675*
	(0.133)	(0.402)	(0.236)	(0.475)	(0.347)
Public research organisation	-1.062***	0.578	-0.046	0.544	0.029
	(0.145)	(0.458)	(0.177)	(0.546)	(0.217)
Other organisation	-1.756***	-1.968***	-0.276	-1.998***	-0.140
	(0.250)	(0.737)	(0.207)	(0.704)	(0.353)
NIH		-2.546	-0.331	-2.430	-0.629
		(2.274)	(0.749)	(2.302)	(0.744)
Other U.S. Fed		1.584	-0.441	1.804	0.343
		(1.437)	(1.090)	(1.265)	(0.823)
Industry		1.789	-0.457	1.973*	-0.519*
		(1.324)	(0.294)	(1.182)	(0.270)
Country	Yes	No	No	No	No
IMR				0.054	-0.309
				(0.160)	(0.353)

	(6) Rare events Engagement	(7) Zinb Success	(8) SDM Success	(9) Zinb with sample selection Success	(10) SDM with sample selection Success
Constant	-3.789***	-5.053***	1.997***	-7.836***	1.175
	(0.129)	(1.457)	(0.332)	(2.048)	(1.307)
chi2		206.59	63.23	171.39	73.62
P-value		0.000	0.000	0.000	0.000
N	26833	832	591	832	591

*Note. Robust standard errors in parentheses; * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. No collinearity according to VIF.*

Considering that organisations have to engage in drug development first before having the opportunity to achieve success in drug development, there may be selection bias in the estimation. In the second robustness check, uses the Heckman (1973) selection model. The inverse Mills ratio (IMR) is calculated according to Table 4.9 Model 2 and used to test the direct (spillover) effect of the basicness and the scientific impact of research on the success of drug development in Model 9 (10). In Model 9, the coefficients of *Basicness* and *Impact* are still positive and significant, which still supports H3 and H4. In Model 10, the coefficients of *Co-operators' basicness spillovers* and *Co-operators' impact spillovers* are similar to the previous model, supporting H5 and H6.

4.7 Conclusions

This investigation explores the effect of two important features of scientific research, namely, basicness and scientific impact, on the two stages of drug development, including engagement and success. Drawing on 14,345 clinical trials on alkylating and immunological antineoplastic agents from 2005 to 2018, research co-operation networks are drawn of clinical trials for 591 organisations and the spillover effect of the basicness and the scientific impact of research is investigated with regard to the success of drug development. It is found that although engagement in drug development is an important concern, only a few medical

research organisations (less than 3%) actually engage in drug development. The lack of applied research is the reason behind this lack of engagement. Applied research fosters organisational engagement in drug development. In drug development process, basic research increases the success rate of drug development. The scientific impact of research not only stimulates the organisation into engaging in drug development, but also provides novel solutions to increase the success rate. In the co-operation network, applied research is easier to transfer and is more successfully exploited than basic research, thus the spillover effect of the basicness of scientific research is negative on the success of drug development. An efficient way to obtain frontier research from co-operators is through co-operation; thus, the spillover effect of the scientific impact of research is positive on the success of drug development.

This investigation improves understanding about which scientific research — basic or applied — leads to engagement and the success of drug development in cancer diseases, and whether high-impact organisations also develop drugs. Methodologically, this study offers a new approach that overcomes the huge computational effort to empirically test these links, exploiting the spatial Durbin model to test the spillover effect in the co-operation network.

This investigation provides organisations and policymakers with recommendations in the medical translational process from scientific research to drug development. Applied organisations always have more confidence to engage in drug development because they have more experience in developing clinical protocols. However, the basic organisations are also necessary in the process of drug development, since their basic research is helpful in selecting promising drugs and conceiving theories following failures in order to improve clinical trials. It is also necessary to encourage organisations with high impact to take part in drug development, as they provide novel knowledge and methods to the process of drug development and

its planning. The co-operation network is a useful source for obtaining external knowledge. Although basic knowledge is too abstract to transfer through co-operation, co-operation is still a useful way to transfer applied research and high-impact research. Thus, policymakers should encourage both basic and applied scientific organisations, especially organisations with high-impact research to take part in drug development. The lack of applied and high-impact research can be made up by co-operators; however, basic research is hard to transfer through co-operation, thus drug developers also need to uphold a strong degree of basic research.

There are also some limitations to this investigation. First, only data from U.S. Clinical Trials Registry is used. However, as most organisations apply for clinical trials in their counties first, some clinical trials registered in other countries have been ignored. Although care should be taken before generalising the results of this study, it is considered that the core mechanisms will also work well in other countries, as the translational processes of drug development are similar. Second, the empirical design does not test for causality, only for correlation. Further research should carry out more regressions to test the results; e.g., with panel data. Third, it was found that applied research is beneficial to the engagement in drug development and basic research is favourable for the success of drug development. However, the optimal basicness of scientific research for drug development has not been ascertained. Further research should engage in additional methods to determine the degree of basicness. Fourth, it is postulated that the differences in success rates are influenced by scientific research. It is the task of future research to make a detailed study to consider the precise effect of co-operation; e.g., the dynamic structure of the co-operation network (Rake et al., 2021).

Chapter 5

Conclusions

This thesis presents three studies on drug development, with a focus on the factors leading to successful drug approval through clinical trials. A clinical trial is a late stage in drug development, which implies that a drug is nearing the market. This thesis reviews the existing literature and presents some lines for future research on clinical trials in the field of Innovation Studies. In addition, it also provides some evidence on new medical product development.

The chapters in this thesis have shed light on various aspects of the analysis of clinical trials. First, a systemic literature review of innovation studies related to clinical trials was undertaken to review existing theories and research topics and find some research gaps (Chapter 2). Subsequently, the following chapters sought to fill some of these research gaps, including exploring the effect of radicalness and cooperation network density on the success of drug development (Chapter 3) and drawing on the cooperation network spillover effect to investigate how to transfer scientific knowledge to drug development (Chapter 4). Below, the specific contents of each chapter are expanded upon.

In Chapter 2, a systematic review of 103 clinical trials-related articles in innovation journals (1984–2021) was conducted. This literature has concentrated primarily on five topics that were categorised in the study as commercialisation, scientific knowledge production, knowledge transfer, institutional frameworks and data gathering computer tools. This literature review provided some suggestions for potential theoretical and methodological advances of future innovation studies related to clinical trials. For example, there is a perceived need to improve the theoretical foundations of future research, e.g., analysing medical innovation through the lens of the life cycle and user innovation theories of drug development. This chapter also made the recommendation for further use of causal, regression and mixed-methods analysis, especially in the topics of commercialisation, knowledge transfer and institutional frameworks, as well as using machine

learning and programming languages in the topics of data gathering computer tools. Finally, the chapter complemented the literature review with a brief overview of the broader literature on drug development, focused on three emerging trends in clinical trials which deserve further attention in Innovation Studies. The main goal of this chapter was to review the existing research topics, theories and methodologies in previous innovation studies related to clinical trials and find research gaps to develop the following two chapters.

In line with the research gap found in the literature review of the need to analyse more factors with a complex relationship on drug development, Chapters 3 and 4 explored the effects of the radicalness of drug development, basicness and scientific impact of research, and density and spillovers of cooperation networks on successful approval in drug development. These two empirical chapters focused on the case of cancer. Cancer was chosen for the following reasons:

1. Cancer ranks among the most dangerous non-communicable chronic disease and the long period from diagnosis to death gives patients some opportunities to attempt treatment with new drugs.

2. The success rate of approval of cancer drugs is lower than that of other drugs.

3. The quantitative analysis of drug development requires huge efforts in manual disambiguation of very large databases, which involves some expertise in particular diseases. Even when focusing on cancer, more than one term is used to refer to specific drugs and types of cancer in clinical trial databases: for example, 5-FU, a drug to treat cancer, is also named 5-fluorouracil or fluorouracil; and brain tumours are also referred to as intracranial tumours. An efficient means of identifying the same drugs and types of cancer with different names is needed. Focusing on one disease increases the feasibility and accuracy of the thesis.

4. Specific knowledge about a particular field also produces insights about idiosyncratic treatments, such as, in the case of cancer, the distinction applied in this study between chemical and biological drugs in drug development.

Chapter 3 explored the effect of radicalness and cooperation network density on the success of drug development at the organisational level. Radicalness refers to the propensity medical organisations have to develop new drugs rather than reuse existing ones. Cooperation network density is defined as the proportion of possible connections between members in the research cooperation network that are actually present. Data on clinical trials related to cancer were gathered from five sources, including the NLM Drug Information Portal, ClinicalTrials.gov, Drugs@FDA, Dietary Supplement Label Database and ChemIDplus. After matching and cleaning the data, the resulting database contained 491 antineoplastic agents, 7,373 organisations and 39,886 clinical trials from 2005 to 2018 in the dataset. The results show that a greater degree of radicalness is less likely to achieve success, and that the relationship between network density and success rate follows an inverted U-shape. In the denser cooperation networks, organisations with high radicalness have a greater possibility of achieving success. Organisations with high radicalness take more risks, which result in more failures; however, an effective way of increasing the success rate of drug development is by promoting cooperation networks. Thus, the results of this chapter are used to analyse the non-linear relationship and interaction of radicalness and network density on the success of drug development.

Chapter 4 explored the effects of basicness and the scientific impact of research on the success of drug development. The basicness of research refers to the extent to which research aims at understanding and predicting natural or other phenomena rather than at solving practical problems. The higher the basicness of

an organisation, the lower its appliedness. Scientific impact reflects the value and quality of scientific research. With regard to networks, Chapter 4 not only analysed the direct effects of basicness and scientific impact on the success of drug development but also further investigated the spillover effects of the two factors through the cooperation relationship, which focus on the effects of the cooperators' basicness and scientific impact on the success of drug development. Publication and clinical trials data were collected for two typical anticancer drugs: alkylating and immunological antineoplastic agents. Computer programming language was applied to link publications and clinical trials data. After cleaning and matching the data, the resulting database consisted of 29,723 organisations with publications and 832 of them carried out clinical trials from 1996 to 2018. Almost 600 organisations participated in clinical trials cooperation networks.

As stated earlier, the basicness of research is the extent to which research aims at understanding and predicting natural or other phenomena rather than at solving practical problems. Research with a high degree of basicness has the advantage of facilitating the incorporation of feedback from patients' reactions to the treatments, preventing organisations from abandoning promising compounds too early. Conversely, research with low basicness (i.e., high appliedness) has the advantage of improving the protocols that clinical trial must follow ("protocols" meaning the documents that explain the objectives, design, methodology, etc. of the clinical trials). The results of the study show that the advantages of high and low basicness are important in different phases of the drug development process (engagement in drug development or approval success). More concretely, it is found that research with low basicness encourages engagement in drug development because, at this stage, producing good protocols for clinical trials is crucial, whereas research with high basicness increases the success rate of drug development because the key is to incorporate feedback from patients' reactions to the treatments.

However, even though the high appliedness (i.e., low basicness) of an organisations' own research may be detrimental for the approval success of clinical trials, the results show that other organisations' research with a high degree of appliedness may be beneficial through network spillovers. It must be kept in mind that organisations cannot freely choose their degree of basicness or appliedness; rather, they are subject to restrictions, and depending on their proportion of basicness and appliedness, they choose partners to complement the advantages and disadvantages of that proportion. Actually, an organisation's degree of basicness in research is dependent on its missions. For example, universities and research centres have the equipment and laboratories to develop basic knowledge, and hospitals provide the conditions to develop applied knowledge. It is hard for organisations to change the institutional dynamics that condition the basicness of research in a short time. Thus, cooperation is a faster means of obtaining external applied knowledge. Applied knowledge is easier to transfer than basic knowledge through research cooperation networks because basic knowledge is too abstract and it is harder for cooperators to understand and exploit it than applied knowledge. Since applied knowledge encourages organisations to participate in clinical trials, and basic knowledge increases the success of clinical trials, promoting cooperation between organisations with high basicness and organisations with high appliedness is an effective way to develop cancer drugs.

Finally, the results show that the scientific impact of research plays a positive role on both the engagement and success of drug development, directly and through network spillovers. Thus, the recommendation stemming from Chapter 4 is that encouraging organisations to foster scientific impact of their research is an effective method to improve the success rate of drug development.

The five theoretical contributions made by this thesis are now detailed. First, Chapter 2 provides guidelines for developing future innovation studies on clinical trials. Through the systemic literature review,

Chapter 2 summarises the existing research topics and subtopics of innovation studies in clinical trials. In addition, Chapter 2 also displays the description of research topics by methodologies, which helps researchers to apprehend the contents from previous studies and develop new research. Second, Chapter 3 provides evidence that internal (radicalness) and external (network density) factors are both important to new product development. The results of Chapter 3 confirm the effectiveness of radicalness and network density on the success of drug development. Third, the non-linear relationships between factors and new product development are also confirmed in Chapter 3, as it finds that the relationship between network density and the success of drug development follows an inverted U-shape, and radicalness and network density play an interaction effect on the success of drug development. Forth, Chapter 4 provides new evidence on the effectiveness of scientific research on new product development, mainly through focusing on the different mechanisms of basicness and scientific impact on the two stages of drug development, including engagement and success. Fifth, Chapter 4 also confirms the spillover effect of scientific knowledge on new product development, which means that the cooperation network is helpful for organisations to acquire external knowledge. Chapter 4 provides a new network view to explore the network spillover effects of basicness and the scientific impact of research on new product development.

Methodologically, this thesis makes three contributions. First, Chapter 3 and Chapter 4 utilise computer programming languages to match publications and clinical trials data. Although computer programming languages have been extensively developed in the field of computer science, new examples are provided to exploit the usage of computer programming languages in the field of innovation studies. Second, Chapter 3 provides a method to represent clinical trial cooperation networks through the “Sponsor/Collaborators” term in clinical trials. This method makes it possible to apply network analysis in innovation studies related to

clinical trials and drug development. Third, Chapter 4 develops a spatial Durbin model through a cooperation network to test the spillover effect of scientific knowledge on the success of drug development, and it provides an example of how to analyse non-linear relationships, especially the spillover effects of basicness and scientific impact of research through spatial models.

This thesis also provides some practical implications. First, according to the findings in Chapter 3, it is suggested that the selection of radical and/or incremental drug development is dependent on the capability of acquiring external knowledge. In a dense network, it is easier for organisations to acquire external knowledge and radical drug development has more opportunities to succeed. Organisations involved in incremental drug development, which pay more attention to enhancing or modifying existing drugs to cure diseases than to developing new drugs, should focus on using their own knowledge and resources instead of wasting effort on increasing their cooperation network density, especially in loose cooperation networks. Second, Chapter 4 suggests that organisations whose research is more basic should be encouraged to participate in drug development, since the results show that these organisations have less interest in taking part in drug development and have more opportunities to achieve success in drug development than those whose research is more applied. Third, Chapter 4 also suggests that organisations with high scientific impact should participate in drug development to provide innovative knowledge and methods to improve the success rate of drug development. Fourth, Chapter 4 also highlights the importance of cooperation networks. Cooperation networks are a useful resource for medical organisations to acquire external knowledge and increase the success rate of drug development.

Three suggestions for future research are summarised here. First, Chapter 2 suggests applying the life cycle theory of drug development and user innovation theory of drug development in future innovation

studies related to clinical trials. The two theories have been discussed in management research, and some of the studies have paid some attention to the differences between different stages of drug development and the importance of patients in clinical trials. However, there is still a need for more studies grounded in the life cycle theory of drug development and user innovation theory to investigate clinical trials-related innovation studies innovation studies related to clinical trials systematically. Second, Chapters 3 and 4 confirm some important factors in the success of drug development with data from the U.S. Clinical Trials Registry, since it has the greatest number of clinical trials in the world. Since clinical trials registered in other countries do not enter into the scope of this thesis, future research could attempt to test the effects of radicalness, cooperation network density, basicness and scientific impact on the success of drug development with a broader dataset. Third, Chapter 4 provides an example of analysing the network spillover effect with a spatial model in a clinical trial cooperation network. In future research, spatial models could be applied and extended in some other types of networks, such as citation networks and co-occurrence networks.

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Appendix

Appendix Table A1 Target studies of the clinical trial in innovation journals

Topic	Article	Key findings
Commercialization	Al Dahdah (2019)	This paper paid attention to mHealth program, and found that the core of this program gradually diverge from scientific methods and evidence production to the market.
Commercialization	Auerswald & Dani (2017)	This paper provided an empirical framework to assess the vibrancy of a regional entrepreneurial ecosystem and map the adaptive life cycle of an industry cluster developing within the ecosystem. It found that the US National Capital Region's biotechnology cluster is in in the conservation phase of its life cycle.
Commercialization	Battard & Sébastien (2019)	This research described the lives of diabetes patients and suggested including patients' experiences to develop new forms of collaborations and organization to take care of patients.
Commercialization	Bers et al. (2009)	This study highlighted the function of Accelerated Radical Innovation model on warming competing technology and overcoming the key barrier in innovation , such as long, expensive, high-risk clinical trials.
Commercialization	Bijker et al. (2016)	Tandems of trust and control play a central role in the successful execution of clinical trials and the construction of scientific knowledge.
Commercialization	Bryde & Joby (2007)	This research provided a new approach based on the concept of Product-Based Planning to manage drug development.
Commercialization	Buonansegna et al. (2014)	This study provided a conceptual framework with seven critical management issues for explaining NPD failures in the pharmaceutical industry, including chaotic and slow patient recruitment, lack of experience in choosing and monitoring partners, lack of feasibility of the study protocol, low quality of the registered data, too high incidence of serious adverse events and severe incidents, unmanageable level of portfolio complexity and incorrect assessment of the market potential or returns.
Commercialization	Callagher et al. (2018)	This study concluded the challenges in commoditizing biotech product process, including regulatory hurdles; rapid changes to legislation; the impact of public opinion; and the difficulties in raising capital, maintaining cash flow and developing a pipeline of opportunities over a long period of commercialization.
Commercialization		
Commercialization	Charalambous & Gittins (2008)	This research investigated the effect of chemically similar of candidate drugs on profitability of companies by C++ program.
Commercialization	Chiou et al. (2016)	This research found that patents associated with successful clinical trials receive more citations than those associated with failed clinical trials. It also finds that failed clinical trials related patents can be cited more often than patents lacking clinical or preclinical information.

Topic	Article	Key findings
Commercialization	Doessel & Sams (1984)	This paper found that cimetidine decreases the number of gastric ulcer operations, however, it does not decrease the number of patients with a diagnosis of duodenal ulcer.
Commercialization	Escobar et al. (2021)	This research demonstrated that telemedicine evolved from a communication medium to complement traditional services to a technology of automation and decision tools.
Commercialization	Favato et al. (2007)	This research found that applying application of parametric cost analysis on pharmaceutical development is an effective approach to reduce the uncertainty and the degree of approximation of the cost estimates.
Commercialization	Fishman (2004)	This research highlighted the importance of clinical trial researchers on the process of commoditizing new drugs.
Commercialization	Gardner (2013)	This article highlighted the importance of clinical assessment tools in shaping technological development of medical device regulation.
Commercialization	Grönqvist & Lundin (2009)	This research found that post-approval head-to-head clinical trials increase expected product differentiation which is benefit for companies but not consumers.
Commercialization	Haeussler & Assmus (2021)	This research found that skills in basic and applied science are both beneficial to get success in clinical trials, especially for publicly funded clinical trials. It also found that experience in multiple disease fields reduces success in clinical trial trials, unless combining with basic research skills and with industry-funded.
Commercialization	Hajiheydari et al. (2021)	This study proposes an integrative theoretical framework that combines system, information and individual positive and negative factors to understand and explain clinical users' skepticism and resistance toward IoMT. We benefit from a multi-analytical approach including symmetrical (net effect) and configurational analysis to test this theoretical framework.
Commercialization	Healy (2004)	This paper found that clinical trial become a marketing strategy which can both transform the perceptions of physicians and shape the understanding on the treatment of uncured patients.
Commercialization	Johnson & Moultrie (2012)	This research developed a technology confidence scale to measure technology viability.
Commercialization	Jung & Pfister (2020)	This research provided a potential "Health AI" application to simplify written informed consent (WIC) and keep WIC secure in clinical trials.
Commercialization	Kenney & Patton (2018)	This study developed an evaluation methodology to evaluate the progress of the California stem cell and suggested that wager on a specific technology is risky in its uncertain early stages and large subnational funding projects also have risks.

Topic	Article	Key findings
Commercialization	Kohli-Laven et al. (2011)	The paper compared the different commercial processes of clinical trials between Onco type DX and MammaPrint and found that Onco type DX started with a commercial platform and commercialize it according to the requirements of users. MammaPrint began with a breast cancer signature and established a company to commercialize it.
Commercialization	Lentacker (2016)	This research suggested that generic drug names become a powerful marketing tool.
Commercialization	Lowman et al. (2012)	This research suggested that outsourcing projects to Clinical Research Organizations bring risks to companies.
Commercialization	Magazzini et al. (2016)	This research found that 1) a positive relationship between market size and firm entry in clinical trials.; 2) the scope of R&D projects influences the selection of target markets; 3) high-risk research areas attract more entry; 4) more flexibility in project duration and delayed project discontinuation attract higher rates of entry.
Commercialization	Mc Namara & Baden-Fuller (2007)	This study found that investors respond positively at every stage from exploration to exploitation in both large and small companies, but there are differences between them. Small firms prefer exploration. Both exploration and exploitation are valuable for large firms. Projects which are part of an alliance are no more likely to generate abnormal returns.
Commercialization	Mehta & Peters (2007)	This research found that outsourcing clinical trials help contract research organizations grow up to independent competitive player.
Commercialization	Oudshoorn (1993)	This article illustrated that clinical trials mediate the relationships between the pharmaceutical industry, the laboratory and the clinic, resulting a network of members to create medical knowledge, drugs and market.
Commercialization	Rake et al. (2021)	This research found that 1) the network of investigators is too fragment to transfer knowledge transfer and advance clinical trials; 2) homophily in research fields and investigators' country of affiliation and heterophily in terms of publication output promote the formation of ties with knowledge translators; 3) multi-connectivity increases the probability of tie formation with knowledge translators while preferential attachment reduces this probability.
Commercialization	Richards (1988)	This research concluded that the methodological reform cannot eliminate necessary social character of medical knowledge.
Commercialization	Richards (1996)	This paper debated over sociology of scientific knowledge's normative role by utilizing a "sociology of monsters" framework.
Commercialization	Rocha et al. (2018)	This research found the risk of phase 3 clinical trials is highest, however, once the drug pass phase 3 clinical trials, it will has a high probability to approval.

Topic	Article	Key findings
Commercialization	Shaw (1985)	This research finds two major reasons for this high level of interaction: (1) the requirement that any equipment that is to be potentially introduced into clinical use first needs clinical assessment and trial; and (2) the 'state of the art' clinical and diagnostic knowledge resides in the user. A special relationship is, therefore, needed between the clinical advisory and trial team on the one hand and the manufacturer on the other.
Commercialization	Styhre et al. (2010)	This research found that in the case of PharmaCo, the use of garbage-can decision making produced four coping strategies on the part of the co-workers, including the strategy to understand organizational politics, the strategy to collect information, the strategy to develop scenarios and the strategy to cope emotionally with the disruptive process.
Commercialization	Thakur-Wernz et al. (2020)	This research found that project complexity increases firms choose captive offshoring instead of domestic in-house sourcing; project stage uncertainty promote firms to use domestic in-house rather than captive offshoring. Firms prefer to choose sourcing according to their prior experience. Domestic outsourcing save more new drug development project costs and duration than the alternative sourcing choices.
Commercialization	Timmermans (2011)	This research found that failed clinical trials is still meaningful, since the failed cases were able to treat people for their drug dependency.
Commercialization	Yaqub (2017)	This research highlighted the importance of testing regime in clinical trials and suggested that product choice and product development need to go hand-in-hand.
Scientific knowledge production	Akcan et al. (2013)	This study classified"Antibiotic Prophylaxis in Surgery" articles into high, moderate or low quality articles and found that the median citation frequencies and journal impact factors between the three quality groups are not significant differences. It suggested that citation frequencies and journal impact factors are not valid instruments for assessing methodological quality in clinical trials.
Scientific knowledge production	Alam El-Din et al. (2016)	This study analyzed Egyptian literature on Hepatitis C virus and proposed a database (HCVDBegy) on MS-SQL server.
Scientific knowledge production	Aleixandre-Benavent et al. (2019)	This research found that there is not a correlation between the value of the impact factor of the journals and their open data policies and opening policies have some changes in the opening policies from 2013 to 2016.
Scientific knowledge production	Ávila-Robinson et al. (2019)	This study highlighted the significance of the diversity of technological possibilities, the role of subjective issues in the selection of directions of search, the complementary nature between established and emerging therapies and the tight product-process interdependencies.
Scientific knowledge production	Brives (2013)	This research used a routine visit in a trial conducted in Burkina Faso to identify the patients and their families as ontologies of scientific research.

Topic		Article	Key findings
Scientific production	knowledge	Cartes-Velásquez & Manterola Delgado (2014)	This study observed that the research productivity is improving in some countries, such as Brazil, China, India and Turkey. The research productivity of Nordic countries is in high levels. The USA lead in terms of overall research productivity.
Scientific production	knowledge	Chapa et al. (2017)	This research found that the predictors, including investigation of Hepatitis C treatment, private funding, mortality-related endpoint and research setting within the United States were different in literature citation and non-academic media coverage. These predictors may affect editorial decisions.
Scientific production	knowledge	Hanisch & Rake (2021)	This research found that drug repurposing is a predominant innovation strategy in COVID-19 clinical trials and the average variety and novelty of clinical trials are inefficient.
Scientific production	knowledge	Hsiehchen et al. (2017)	This research characterized the evolution of disease specific biomedical research and assessed the alignment of research and translational efforts with disease burden.
Scientific production	knowledge	Ippoliti et al. (2021)	This research found that there are substantial differences in the ability of distinct research organizations to foster innovation and the research organizations with the collaborative solution more likely to be productive.
Scientific production	knowledge	Kostoff (2007)	This paper described the numerical, organizational and medical characteristics of research articles in The Lancet over three years.
Scientific production	knowledge	Ngayua et al. (2021)	This research found that the number of clinical trials related publications in applied artificial intelligence, machine learning, deep learning and the internet of things has been increasing since 2010 and empirical approach are progressively embraced in these studies.
Scientific production	knowledge	Ojasoo et al. (2001)	This research found that although the production trends between publications and clinical medicine are broadly consistent, there are periods of erratic activity.
Scientific production	knowledge	Pal (2021)	This research analyzed the medical research areas and affliction locations by the COVID-19 related publications. The sequence of an RNA virus studies increased a lot and the collaborating authors are diversity in geography.
Scientific production	knowledge	Peritz. (1994)	This research found that authors prefer cite large studies rather than smaller ones and the inclusion of a placebo in the study design does not affect citation frequency.
Scientific production	knowledge	Romero et al. (2009)	This research found that citations per document is higher in clinical trials related publications than those for conventional papers; the journal impact factor is lower in clinical trials related publications. Finally, both relative h-index and strike rate index are not influenced by clinical trials citations.

Topic	Article	Key findings
Scientific knowledge production	Saquib et al. (2018)	This research finds the quality of scientific research has improved in Saudi Arabia on type 2 diabetes mellitus over time.
Scientific knowledge production	Thelwall & Kousha (2016)	This paper supported prior articles referenced in ClinicalTrials.gov records are more highly cited than average for the publishing journal.
Scientific knowledge production	Wang et al. (2020)	This research found that the publications recommended by F1000 Faculty members were cited significantly more than other articles in JAMA, The Lancet and NEJM, but no significance was found between the two sets of articles in Cell. In addition, F1000Prime rating scores did not reveal any patterns for predicting citation trends of these publications.
Knowledge transfer	Bourret et al. (2006)	This study examines the founding and development of a French bioclinical collective—the Groupe Génétique et Cancer (GGC)—that coordinates and structures the activities of most French actors in cancer genetics and operates simultaneously in the clinical, research and regulatory domains.
Knowledge transfer	Grossman et al. (2001)	This research supported that academic research has made substantial contributions in aerospace; financial services; medical devices; network systems and communications; and transportation, distribution and logistics services. The contributions included training graduates, providing key ideas of basic and applied research and developing tools, prototypes, products, processes and services.
Knowledge transfer	Leonelli (2012)	This paper identified and discussed four key problems to integrating human and non-human data within the same database: (1) picking criteria for reliable evidence, (2) selecting metadata, (3) standardizing and describing research materials and (4) choosing nomenclature to classify data.
Knowledge transfer	Robinson et al., (1985)	This research highlighted the importance of bridging the knowledge gap between gene researchers and general practitioners to improve knowledge transfer.
Knowledge transfer	Wadmann (2014)	This research concluded that appreciation of the ways in which economic and moral valuations come together is necessary to understand the conditions for medical research in an intertwined public–private research environment.
Knowledge transfer	Zvonareva (2021)	This research argued that the clinical trials exclusively focus on establishing similarity between the trial and the clinic for greater generalizability and ignore consistency between medical experimentation and the conditions, needs and concerns in the clinic.
Institutional frameworks	Abraham & Davis (2009)	This research found that both UK and the USA adopted permissive principle and permissive regulation of specific drugs should not be regarded as an inevitable result of marketing strategies.

Topic	Article	Key findings
Institutional frameworks	Adams (2002)	This research found that the state often intervenes to criminalize practitioners of alternative medicine, when 'medical facts' must be derived from 'magical beliefs' in the centers of biomedical science. In contrast, when 'the magical' sells get profits in alternative medicine, the state also makes it possible to shift ownership of medical knowledge, sometimes by the randomized controlled trial and the pursuit of active ingredients.
Institutional frameworks	Brenman & Milne (2021)	This paper found that the temporal state of readiness is determined by the biologies and psychologies of individual cohort participants, intervention owners and the trial infrastructure itself.
Institutional frameworks	Brunet (2017)	This research found that establishing a principle 'prohibited with derogation to be seen' led the State to implement a low-key policy: limited, hidden and delegated.
Institutional frameworks	Crane (2010)	This paper found that claim too forceful either on difference from the global North or on assertions of sameness can lead undermine the ethical by the case of HIV research.
Institutional frameworks	Christensen et al. (2007)	This paper argued that both the modality of therapy (drugs, devices and procedures) and the stage of technological evolution are important determinants of an optimal evaluative design. The practicality of conducting a randomized clinical trial is inversely proportional to the complexity of the healthcare intervention.
Institutional frameworks	Curreli et al. (2008)	This research found that safety and clinical efficacy testing, compliance with regulations and adequate protection of intellectual property for commercialization are important to realize the benefits oncology nanodevices.
Institutional frameworks	Davis (2020)	This article argued that in making sense of the interplay between adherence to a prophylactic regimen and risk for HIV, biomedical HIV prevention research has revealed Homo adhaerens, a new subject of biopolitics and poor adherence lead pre-exposure prophylaxis clinical trials produce knowledge is not useful for the most vulnerable patients.
Institutional frameworks	Epstein (1995)	This article examined the mechanisms or tactics of constructing credibility by lay activists to AIDS researchers and government officials.
Institutional frameworks	Epstein (1997)	This paper found that the politics of AIDS therapeutic turn to be complex with evaluation participation of AIDS activists in claims-making about AIDS trials and AIDS drugs, even as the monopolization of credibility by credentialed researchers get challenges from it.
Institutional frameworks	Epstein (2008)	This research highlighted the tensions underlying projects to eliminate health disparities by race.
Institutional frameworks	Fisher (2015)	This research presented that the application of parametric cost analysis to pharmaceutical development can help reduce the uncertainty and the degree of approximation of the cost estimates.

Topic	Article	Key findings
Institutional frameworks	Grant (2016)	This research argued that this shift in the object of ethical concern, from the experimental human subject to the relation between subjects and researchers, illustrates how a postcolonial field of articulation reformulates classical bioethics.
Institutional frameworks	Hedgecoe (2014)	This research focused on the high-profile drug disaster at London's Northwick Park Hospital in 2006 to explore how such an event can be seen as an example of organizational deviance co-constructed between the company running the research and the research ethics committee which approved the trial.
Institutional frameworks	Jasanoff (2002)	This paper argued that the attempt to marry judicial concerns for individual justice with administrative concerns for speed, efficiency and economy has produced anomalous results using silicone gel breast implant litigation as a case study.
Institutional frameworks	Krimsky (2013)	This article argued that the "funding effect" is one of the factors for outcome disparities in product assessment.
Institutional frameworks	Löwy (2016)	This paper suggested that it is important to pay more attention to 'normal' medical science and routine clinical practice rather than criminal activities of doctors to prevent the numerous ethical transgressions in medical,
Institutional frameworks	Malik (2019)	This research showed that diabetes and infectious diseases projects exist more in India; cancer, hepatitis and hypertension projects exist more in China; there are more respiratory dysfunction project in India than China. The North and South regions have some statistical differences.
Institutional frameworks	Marks (2011)	This research argued that reflexivity increases the trust between science and public trust.
Institutional frameworks	Merz (2020)	This research illustrated that the Euro-American affiliations are the universal body to implement clinical trial methodology; Indian participants not only need to be made globally comparable but also aligned with the drugs' future consumers.
Institutional frameworks	Montgomery (2012)	This research argued that there is nothing inherently gendered about this 'woman-controlled' technology.
Institutional frameworks	Montgomery (2017)	This research argued that standardizing in material objects may be antithetical to sustainable and relevant clinical research.
Institutional frameworks	Nik-Khah (2014a)	This research argued that Healy et al. mischaracterize Lasagna's ideas which is he only to increase the scientific stature of the physician–patient encounter.
Institutional frameworks	Nik-Khah (2014b)	This research argued that scholars of the Chicago School of Economics also constructed highly influential drug development institutions, such as Center for the Study of Drug Development, to influence pharmaceutical policy and science.

Topic	Article	Key findings
Institutional frameworks	Petty & Heimer (2011)	This research argued that clinical trials shape medical practice by altering the medical treatment and clinical trials organizations with three key processes, including modifying material environments, reorganizing bureaucratic relations and prioritizing of research values. These processes unfold somewhat differently in the clinics of poorer countries than in those of wealthier ones.
Institutional frameworks	Rayzberg (2019)	This research found that geographic separation, temporal delay and public randomization ceremonies are the functions to solve the ethics of resource allocation.
Institutional frameworks	Rodríguez (2010)	This research found that slow regulatory reforms, insufficient empowerment of regulatory agencies and disconnection among agents increase the risks of unethical behavior in clinical research.
Institutional frameworks	Rosemann & Chaisinthop (2016)	This research found that the absence of internationally harmonized regulatory frameworks in the clinical stem cell field and the presence of lucrative business opportunities have resulted in the formation of transnational networks adopting alternative research standards and practices.
Institutional frameworks	Salandra (2018)	This research found that the percentage of selective reporting is higher for industry-funded studies than for publicly funded studies. In addition, compared with incremental innovation, radical innovation is more likely to choose selective reporting.
Institutional frameworks	Schneider et al. (2020)	This paper found that biased knowledge is spreading by falsifying data 11 years after the fraudulent clinical rial report was retracted.
Institutional frameworks	Simpson & Sariola (2012)	The article argued localization resolves conflicts between the standards of clinical trials and existing epistemic virtues.
Institutional frameworks	Sleeboom-Faulkner (2016)	This research highlighted that 1)A large grey area joins ‘rogue’ and ‘bona fide’ stem cell applications, 2)The grey area covers stem cell experimentation with and without formal approval, 3)Entrepreneurial scientists can (mis-)use experimental spaces for stem cell innovation. 4)Bionetworks forge ethical practices contingent to local needs and global demands, 5) Stem cell application enables economic and scientific development in China.
Institutional frameworks	Struhkamp et al. (2009)	This research found that knowledge is aggregated through the interactions between doctors and patients in long-term treatment and daily life.
Institutional frameworks	Van Der Zaag (2017)	This research argued that the intrinsic ambiguity between the field’s feminist promise of empowerment and the effects of the biomedical search for an effective microbicide candidate in the case of Nonoxynol-9.
Institutional frameworks	Will (2009)	This article found that medical uncertainty does not lead to inertia on treatment and physiological principles and moral values are the solutions to guide treatment.

Topic	Article	Key findings
Data gathering computer tools	Azoulay et al. (2006)	This study presented Publication Harvester, an open-source software tool for gathering publication information on individual life scientists.
Data gathering computer tools	Bornmann (2018)	This study presented Dimensions, a research data infrastructure and tool, including grants, publications, citations, clinical trials and patents in one place.
Data gathering computer tools	Decullier et al. (2021)	This research found that trials tracker greatly underestimated the number of publications. All actors should therefore contribute to improving the visibility of clinical trial results by providing NCT numbers for all publications (investigator) and by updating clinicaltrials.gov (sponsor and investigator).
Data gathering computer tools	Herzog & Lunn (2018)	This study introduced Dimensions, a software to bring formerly siloed content types such as grants, patents, clinical trials with publications and citations together, making it as openly available as possible (see app.dimensions.ai).
Data gathering computer tools	Lightet al. (2014)	This paper introduced a database-tool infrastructure that was designed to support big Sci2 studies. Results show that temporal analyses scale linearly with the number of records and file size, while the geospatial algorithm showed quadratic growth. The number of edges rather than nodes determined performance for network based algorithms.