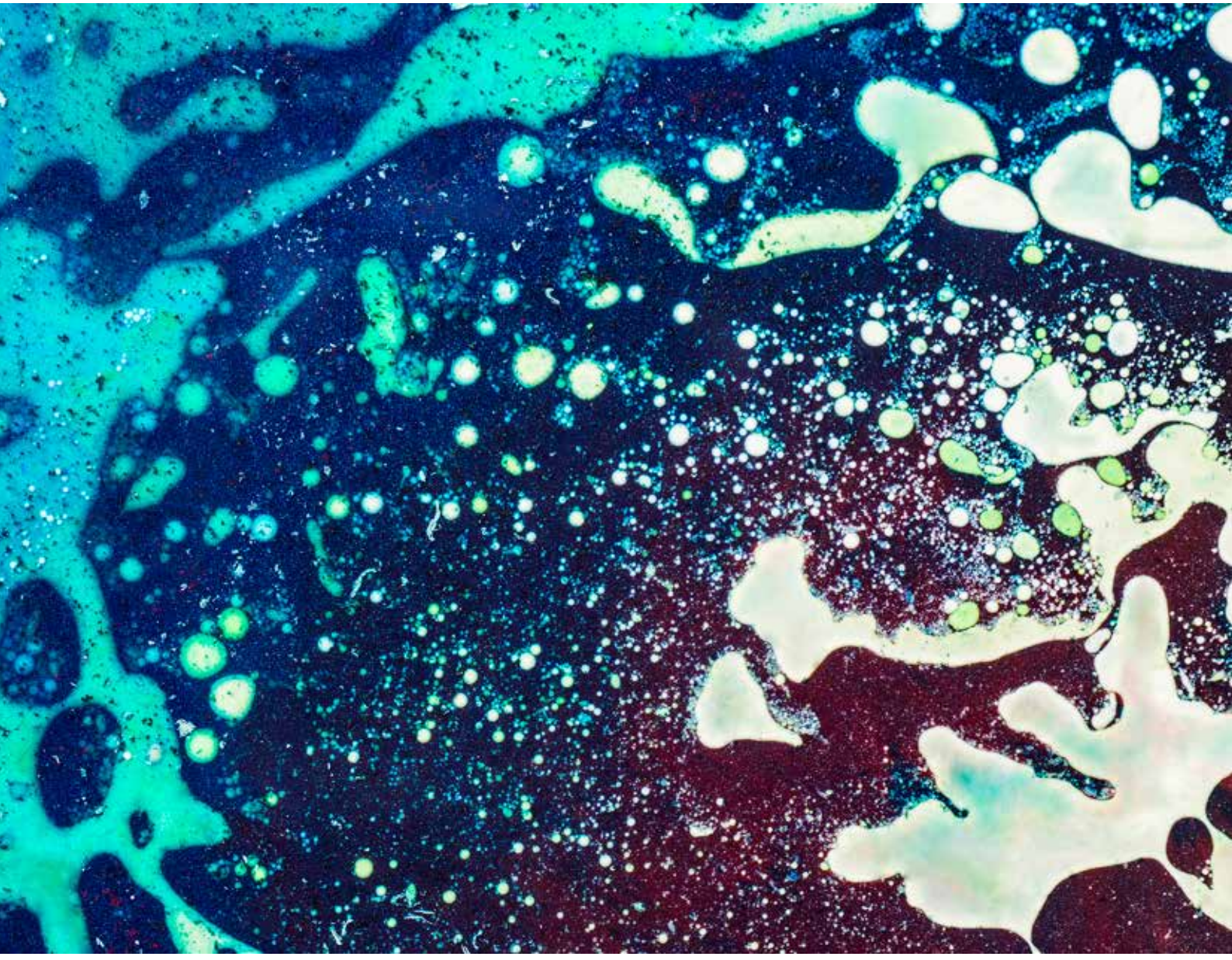
The Economist INTELLIGENCE UNIT | HEALTHCARE

The Innovation Imperative:
The Future of Drug Development
Part I: Research Methods and Findings

A report by The Economist Intelligence Unit



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1. Introduction

The research and development (R&D) pipeline is a significant expense for pharmaceutical companies. Despite the need for more innovation, R&D productivity has stagnated or fallen over a number of years.[1-3] To date, the industry has not comprehensively assessed the impact of new innovations in drug development and market access—especially in terms of critical success metrics such as clinical trial efficiency, likelihood of drug launch and patient access.

To galvanize action on this critical issue, The Economist Intelligence Unit (EIU) gathered and interpreted hard evidence on the impact of selected innovations measured against specific success metrics. The overall goal of the study is to stimulate broad discussion on how the industry can use innovative approaches in drug development and market access to improve efficiency, rekindle productivity and restore sustainability.

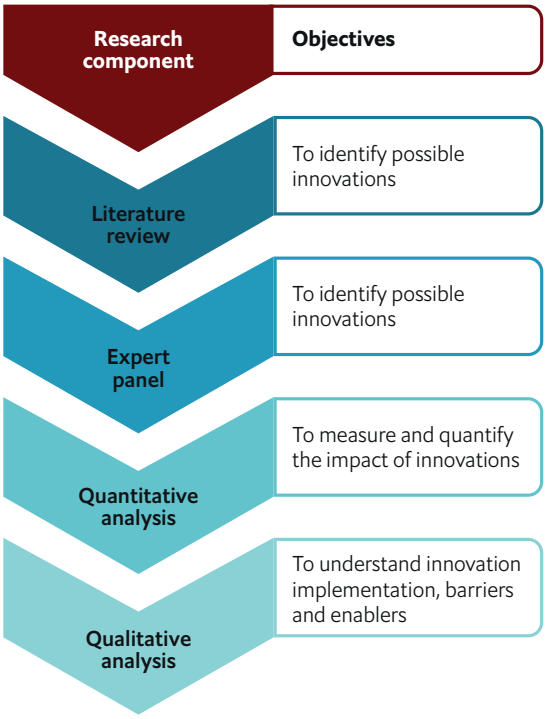
The Innovation Imperative: The Future of Drug Development is an Economist Intelligence Unit report commissioned by PAREXEL. The report is made up of two components—a technical report that details the quantitative analysis, and a corresponding narrative report that captures expert insight on industry dynamics. This Part I report, *Research Methods and Findings*, describes the methods and findings of the quantitative study that the EIU conducted around drug development and market access data. It is distinctive in publicly quantifying the impact of the most promising innovations in drug development on trial efficiency and success in launch and obtaining formulary approval worldwide. We propose that it makes a compelling, data-driven case for accelerating the adoption of new market access processes for drugs. Specifically, it shows that the four innovations evaluated—adaptive trial designs, patient-centric trials, precision medicine trials and real-world data trials—consistently deliver against industry success criteria.

The complementary Part II report, entitled *Barriers, Enablers and Calls to Action*, puts these results into context and investigates the wider landscape through discussions with key opinion leaders to provide an understanding of the barriers to and facilitators of the implementation of innovation. These insights provide perspective around the hesitancy that has characterized adoption of new models and approaches in drug development.

2. Approach and methodology

The EIU undertook a research program designed to identify the most promising innovations in drug development and market access and to quantify their impact against key success criteria using trial, launch and formulary-addition data in China, the European Union (EU), Japan and the United States (US). An overview of the entire research program is shown in Figure 1. Additional details about the expert panel, chosen innovations and therapy areas are provided in the Appendix. We provide here a brief overview of the three stages of the program relevant to this report: 1) literature review, 2) expert panel and 3) quantitative analysis.

Figure 1: The research stages of the program



Literature review

The EIU conducted a review of published literature (across MEDLINE, Embase and Scopus) and grey, unpublished sources to identify the key issues and potential innovations for inclusion in this study. The review revealed that the performance of innovative drugs (for example, new molecules) was already well covered in the literature, whereas innovations in drug development were less so—a view supported by the expert panel advising this project. It was therefore determined that this project would be most valuable if it focused on innovations designed to improve the development and market access of drugs. The literature review was also used to create a longlist of innovations for the expert panel to consider.

Expert panel: selection of innovation areas, success metrics, markets and therapy areas

The EIU worked with a cross-disciplinary panel of experts in drug development to review the longlist of innovations. Four areas of innovation emerged in the panel discussion as the most promising in terms of ensuring sustained and beneficial improvement in drug development and thus the most worthy of quantitative investigation: [i]

1. **Adaptive trial designs:** trials that incorporate pre-specified modifications into the protocol, allowing for changes once the trial is in progress based on interim data analysis.
2. **Patient-centric trials:** trials that are designed specifically around patient needs, include patient-reported outcome measures, or are co-designed with patients.

i Those areas of innovation on the shortlist that did not make it through to the final cut included drug repurposing, gated development and virtual R&D.

3. **Precision medicine trials:** trials that test precision medicines, including the use of genotyping and biomarkers to identify patient groups likely to respond to the therapy.
4. **Real-world data (RWD):** trials that include one or more measures of a therapy's impact in real-world settings, rather than just in the trial environment.

These are umbrella terms, in that within each of the four areas of innovation, a number of related trial processes or analyses are included. For example, adaptive trial designs include umbrella or basket designs; patient-centric trials include those co-designed with patients and those that use only patient-reported outcome measures; and RWD trials include both trials using registry data and those using digital health-monitoring devices. These umbrella terms were used partly because of the limitations of the search interface in trial databases, but also because the breadth of innovative approaches used within them allows us to say something about the impact of innovation as a whole. The selected innovations also represent a balance between being new enough to be considered innovative, yet sufficiently established that data are available for the quantitative analysis. This is important methodologically, as trial data were needed to quantify the impact of these innovations.

The panel considered metrics of success to investigate the impact of innovations, selecting the following:

1. **Trial efficiency:** calculating total trial time, and time taken for participant recruitment (enrollment) and treatment.
2. **Drug launch:** calculating the likelihood that drugs will be launched in the market.
3. **Formulary or market access approval:** assessing the likelihood of incorporation into key formularies, reimbursement lists or other national databases representative of market access.

These metrics were chosen because they encompass both drug development and market access, thus representing important success criteria for the industry. Details of the methods for identifying the data used in this project and our calculations are provided in the Appendix.

The project's scope is global, but to explore any differences in the impact and implementation of these innovations across different countries we selected four key markets in order to segment our analysis: China, the EU, Japan and the US. These geographical areas represent large established or emerging markets that are key targets for many drug developers. The analysis explored how innovative and non-innovative trials performed against the success metrics in these markets, compared to the rest of the world.

The research program further explored the impact of the four innovations in three therapy areas. These were identified by the expert panel and subsequently prioritized based on the wealth of ongoing research and innovative techniques used within these therapy areas. They are:

1. **Neurology**
2. **Oncology**
3. **Rare diseases**

The therapy areas were validated by the expert panel as representing key challenges in terms of drug development and market access, such as large or small affected populations, or the prevalence of high drug costs.

Quantitative analysis

The EIU explored the impact of the selected innovations on drug development and market access using the metrics described. The impact of each innovation was analyzed retrospectively using trial and drug data:

- **Trial time** analysis included ~4,000 phase II and III trials ending between 2012 and 2017 that used the selected innovations, compared to a control group of ~20,000 trials from the same period that did not use the selected innovations. We calculated overall trial time, accrual time and treatment time using Trialtrove® data. (More information about Trialtrove® is provided in the Appendix.)
- **The success analysis** looked at ~1,500 drugs developed using the selected innovations and a control set of ~ 4,000 drugs developed without using these innovations. We calculated likelihood of launch from phase II and III using methods based on those used by Thomas *et al*, with data from Pharmaprojects®.[4]
- **Market access** was explored to identify whether new molecular entity drugs developed using the selected innovations and approved in 2015, 2016 or 2017 had been added to key formularies or other national market access lists by January 2018, compared to drugs approved in the same years that did not use these innovations. The numbers of drugs in the analysis were as follows: 260 in the EU, 115 in the US and 178 in Japan.

3. Key findings

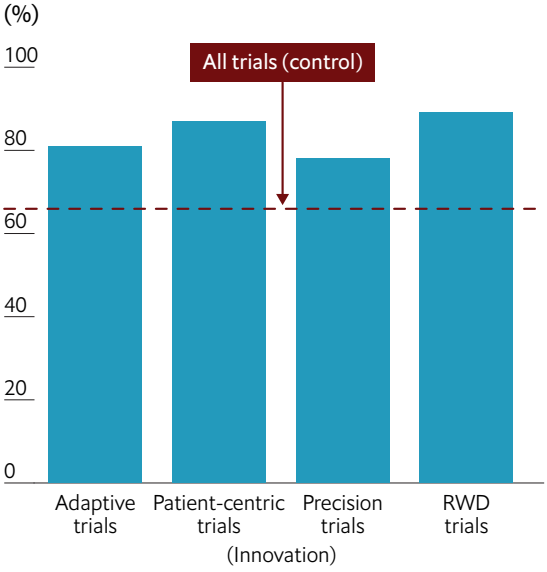
Here we describe the most important findings across the research program. Please refer to subsequent sections for more detailed analysis, including geographical and therapy area drill-downs.

Drugs developed using innovative trials are more likely to be launched

Most strikingly, the data indicate that all four selected innovations—adaptive, patient-centric, precision medicine and real-world data (RWD) trials—improve the chances of drugs being launched.

- Drugs developed using the selected innovations showed a 10-21 percentage point increase in phase II and III likelihood of launch compared to drugs developed without using these innovations.
- Likelihood of launch was 13 percentage points higher for adaptive trials than for all trials (control), while for patient-centric trials it was 19 points higher, for precision medicine trials it was 10 points higher and for RWD trials it was 21 points higher (Figure 2). This pattern was echoed across all three therapy areas of neurology, oncology and rare diseases.
- The difference in likelihood of launch between innovation and non-innovation drugs was largest in oncology, where innovation drugs had a 33 percentage point greater likelihood of launch (86% vs 53%). The likelihood of launch for innovation drugs exceeded that for non-innovation drugs in all therapy areas by 16 percentage points (84% vs 68%), in neurology by 23 percentage points (86% vs 63%) and in rare diseases by 3 percentage points (88% vs 85%).

Figure 2: Phase II and III likelihood of launch for four innovations



Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

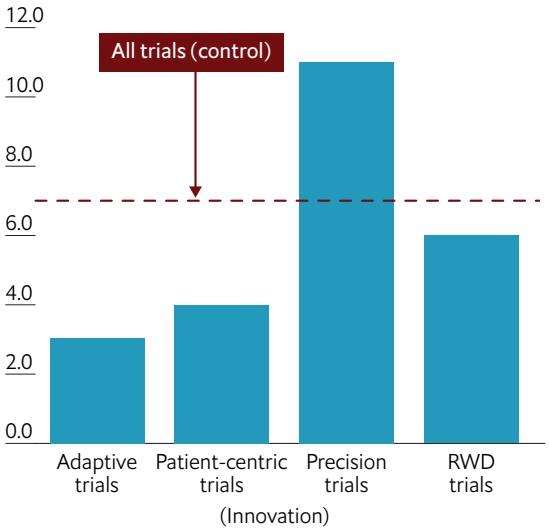
Trial efficiency is improved by the adoption of innovative trial types

Most innovations improved trial efficiency, although impact varied according to innovation type and therapy area. When averaged across all three therapy areas, adaptive, patient-centric and RWD trials had the shortest times to recruit 100 participants (at three, four and six months respectively)—shorter than our all-trials benchmark of seven months. On the other hand, precision medicine trials took

longer on average than the benchmark (Figure 3). However, when looking at precision medicine trials in oncology, neurology and rare diseases, recruitment times per 100 patients were shorter than the respective therapy-area benchmarks.

The greatest difference in time to recruit 100 participants was in rare diseases, where innovative trials reduced recruitment time by 40% (from 30 to 18 months). Average time saving was 37% in both oncology (from 19 to 12 months) and neurology (from 11 to 7 months).

Figure 3: Average time to enroll 100 participants for four innovations
(months)



Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Innovation has a foothold everywhere

Innovative trials are being carried out across the globe. In terms of the total number of trials, the EU and the US contributed the greatest proportions of trials within each innovation area, at 33-34% and 36-46% respectively. China and Japan contributed 1-6% and 3-11% respectively. The rest of the world contributed 11-22% of innovative trials. However, China, Japan and the EU combined conducted fewer trials than the US. Taking that into account, the figures reveal that greater proportions of trials in China, Japan and the EU were innovative than in the US.[ii]

Looking at specific innovation types, the EU and the US contributed 34% and 38% of patient-centric innovative trials respectively, while China and Japan contributed 5% and 9% of trials respectively. The figures were similar for precision medicine trials: the EU, the US, China and Japan conducted 34%, 38%, 6% and 11% of trials respectively. There were too few RWD and adaptive trials to conduct meaningful analyses across geographies.

Innovation-using drugs are more likely to be adopted by payers

Drugs developed using these selected innovations are viewed favorably by payers. Drugs approved in 2015-17 that had been developed using one or more of the selected innovations were more likely than non-innovative drugs to have achieved formulary addition by 2018.

Eight formularies were examined: six US formularies, the British National Formulary (BNF) and the National Health Insurance Drug List in Japan. We found that drugs developed using innovative methods generally make their way on to the lists more quickly. Differences are small to moderate, but a trend emerges of earlier listing for drugs that have been developed using innovative trials. While having drugs listed on formularies is not the only factor involved in getting new medicines to patients (as other matters, such as co-pay and limited coverage, will affect access), this approach offers an insight into the route to market of drugs after regulatory approval.

ii An analysis of trials registered on the International Clinical Trials Registry Platform (ICTRP) 2004-2013 found that 69% of all trials were conducted in the US, 12% in the EU, 7% in Japan and 2% in China.[5] That calculation includes all trials, whereas our analysis focuses on phase II, II/III and III trials. In the ICTRP, 25% of trials are phase II, II/III and III trials, but 53% do not specify what phase trial they are.

There is no "one-size-fits-all" strategy; trade-offs are required

The findings indicate that the optimization of innovations in drug development requires the ability to identify and balance nuances and trade-offs, rather than employing a "one size fits all" strategy. For example, while precision medicine trials sometimes take slightly longer to recruit patients than other trials, they have a much higher likelihood of launch. As an added complication, figures often vary across therapy areas and geographies. These results suggest that an informed and sophisticated strategic approach to applying these innovations is required in order to maximize their impact.

4. Adaptive trial designs

"Why all this love for adaptive trials? You have the ability to learn so much more about response to a drug or a device by being more flexible… What you don't want to do is pick a dose, do the study, and then go, 'Shoot, it didn't work. Should have used a higher dose.'"

William Barsan, emergency physician at the University of Michigan in Ann Arbor[6]

Adaptive trial designs enable trialists to pre-specify potential changes to the study protocol that can be implemented as needed. Protocol changes can include adjusting the sample size, drug dosage and patient selection criteria. The flexibility to make such changes is designed to reduce waste by allowing trialists to adapt their trials based on emergent findings, where trials might otherwise be terminated. Two adaptive trial designs commonly described are "basket" and "umbrella" trials, often seen in oncology drug trials. Basket trials are those in which the same drug is tested in different types of cancer, while umbrella trials test multiple treatments in different treatment arms, with participants allocated to a treatment based on the type and molecular make-up of their cancer.[7] Seamless trials (also called combined-phase studies) are the ultimate destination of the adaptive trial philosophy: rather than conduct several separate trials for each phase, a single "seamless" adaptive trial is designed in which the phases are separated only by interim analysis. This may save time and money in development by reducing the number of patients required, as a seamless trial can use the same cohort throughout, rather than recruiting multiple cohorts to separate trials.

Adaptive trials are increasingly being accepted by regulators. In 2010 the US Food and Drug Administration (FDA) published draft guidance on adaptive trials in regulatory approval submissions, and in 2016 the China Food and Drug Administration (CFDA) did the same.[8,9] There are a number of recently approved drugs that have used one or more adaptive trials in their route to regulatory approval. In May 2017 the FDA granted accelerated approval of Keytruda (pembrolizumab) for adult and pediatric patients with unresectable or metastatic solid tumors and mismatch repair deficiency (a rare biomarker indication) partly based on KEYNOTE-158, a basket trial comprising five single-arm trials and involving a total of 150 patients.[10-13] In November 2017, the FDA also approved Zelboraf (vemurafenib) for Erdheim-Chester disease with BRAF V600 mutation based on a basket trial—the first targeted therapy to be approved based on a basket trial.[14-16] The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) has also approved a number of drugs based on adaptive trials.[17] The EU's European Medicines Agency (EMA), the FDA and the PMDA have all purchased the ADDPLAN® software program, which uses data to design, simulate and analyze adaptive clinical trials, including sequential adaptive designs, population enrichment design and dose-finding designs to support the assessment of adaptive trial evidence by regulators.[18]

An established innovation, but not yet mainstream

Adaptive trials first emerged in the 1990s, but it has taken time for this innovation to make the transition from theory into practice. However, the number of clinical trials using adaptive designs has been rising in the past ten years, and there are far more adaptive clinical trials cited in PubMed compared to the other innovations included in this study (Figure 4). Yet we identified few adaptive trials (107) in Trialtrove® using relevant built-in keywords. The reasons for this are unclear, but could be because Trialtrove® keywords are manually applied, so that their application may not be comprehensive.

The recent plateauing of the number of adaptive clinical trials in PubMed suggests that this innovation is reaching established status. Nevertheless, adaptive trials continue to make up only a small proportion of the total number of clinical trials in PubMed (roughly 2.6%), suggesting that there is room for greater implementation of this innovative study design.

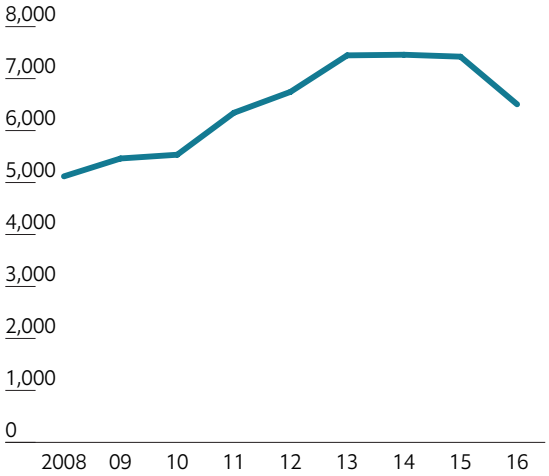
In our sample of trials from Trialtrove® the EU and the US contributed most adaptive trials, at 33% and 36% of the total number respectively, with Japan and China contributing 8% and 1% respectively (Table 1). Oncology is the largest therapy area for adaptive trials, accounting for 54% of adaptive trials in the US, EU, China and Japan and 32% elsewhere (Figure 7).

Table 1: Number of adaptive trials across geographies.

Geography	No. of adaptive trials	% of all adaptive trials
China	2	1
EU	62	33
Japan	14	8
US	67	36
Rest of world	41	22

Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-17.
Note that whereas the total number of adaptive trials in our sample is 107, the total listed in this table exceeds that number due to trials taking place across multiple countries.

Figure 4: Number of clinical trials citing adaptive trial design in PubMed
(No. clinical trials)



Source: PubMed, 2018. Data: 2008-2016.

Adaptive trial designs improve likelihood of launch, particularly in oncology

Drugs developed using adaptive trials had a phase II/III likelihood of launch of 81%, 13 percentage points higher than the likelihood of launch for non-innovative trials (Figure 5). The likelihood of launch for adaptive trials was similar across therapy areas, with the exception of rare diseases, where the likelihood of launch for adaptive trials was below that of the control group (67% vs 85%). However, the limited number of cases for rare diseases, at just eight, restricts our ability to draw firm conclusions.

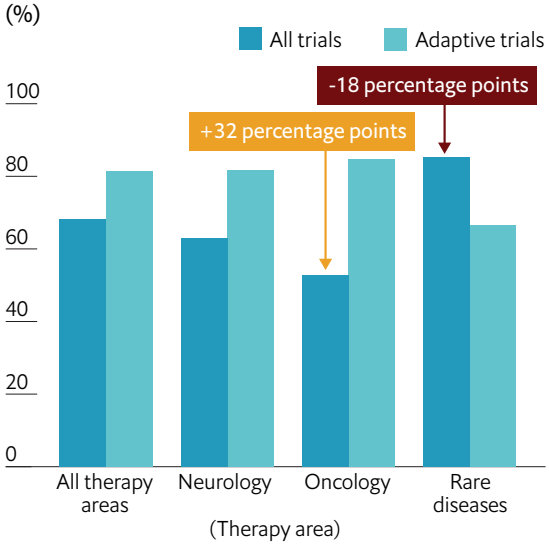
Enrollment times are generally short but vary by therapy area and geography

Adaptive trials took less time on average to recruit 100 trial participants (2.8 months) than control (non-innovative trials; seven months) (Figure 6).

Enrollment times were a little longer in our specific therapy areas, but were still shorter than in control trials. Adaptive neurology trials took 6.8 months to recruit 100 participants, compared to the control (non-adaptive neurology trials) of 10.6 months, while adaptive oncology trials took 8.3 months vs the control of 18.7 months and adaptive rare disease trials took 18.2 months vs 29.7 months.

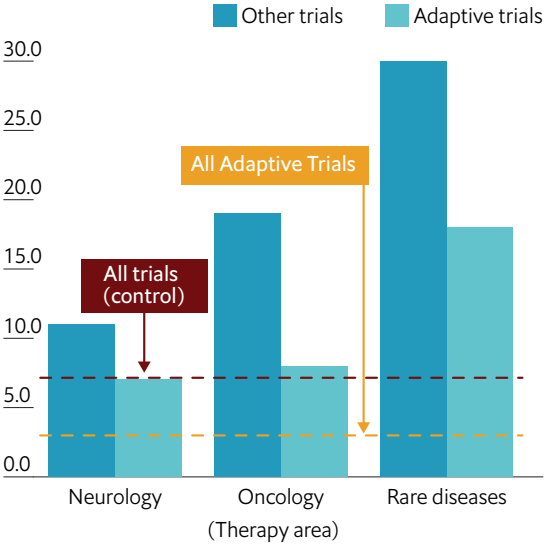
Looking across geographies, the time required to recruit 100 participants in the US, the EU and Japan is shorter than in China and elsewhere (Figure 9), although longer average enrollment times were associated with smaller trial sizes (lower average accrual numbers). However, as noted above, the total number of adaptive trials is small, limiting the certainty of any conclusions that we can draw. Average enrollment time and treatment duration as a proportion of average total trial time are similar across geographies (Figure 8).

Figure 5: Phase II and III likelihood of launch



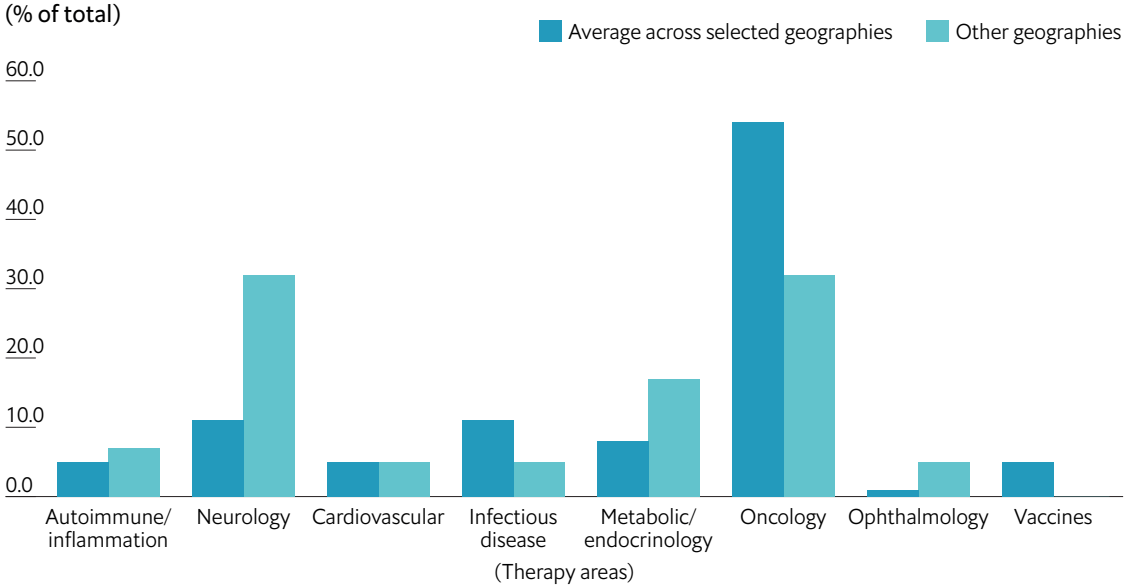
Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Figure 6: Average time to enroll 100 participants for adaptive trials vs all trials



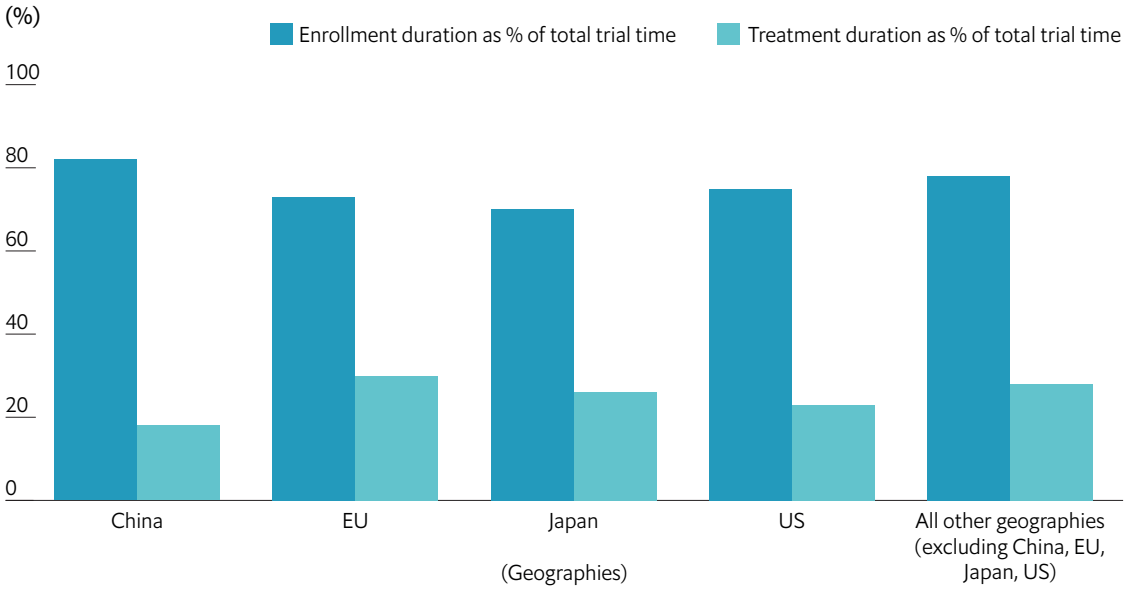
Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Figure 7: Adaptive trials therapy areas by geography



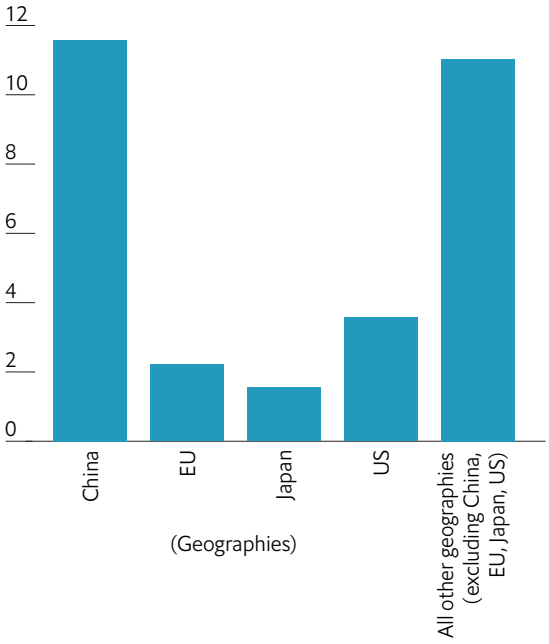
Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 8: Adaptive trial enrollment and trial treatment duration



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 9: Time to recruit 100 participants
(months)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

5. Patient-centric trials

"I see recruitment as being a by-product of good patient engagement… Patients should become part of the process, and that translates into them signing up for the project and being included. It can't just be tokenism."

Deborah Collyar, President, Patient Advocates in Research (PAIR)[19]

Patient-centric trials—as we have defined them for this project—are those geared towards involving patients in design and execution. Patient-centric trials are designed to improve relevance to patients and, in so doing, to encourage patients to take part in trials.

Studies in the UK and the US have found that only a third of trial sites meet their accrual targets and around half are forced to extend their enrollment periods.[20] Trials can fail to recruit participants because of overly restrictive inclusion/exclusion criteria, heavy burdens on participants (large numbers of visits, tests, etc.) or a focus on outcomes that are not relevant to patients.[21] Engaging patients in trial design and execution could improve accrual by making trials more appealing to take part in (for example, by using remote data collection through wearables) and by tapping into patient networks to spread the word about well-designed trials.

There are several initiatives under way across different geographies to improve the focus on patients within drug trials. For example, the Japan Primary Registries Network (JPRN) website was set up to provide patients with a portal through which they can find out about ongoing research in Japan and learn more about trials and how they can participate.[22] The JPRN was envisioned as a patient-centric portal from the outset, in recognition of the need to engage directly with patients in a friendly manner to encourage participation in clinical trials. In the US, the Patient-Centered Outcomes Research Institute (PCORI) has funded numerous patient-centric trials, including 79 trials in cancer and 69 in neurology, since 2012.[23] The PCORI Methodology Standards aim to drive up the quality of research and include specific recommendations around engaging patients as stakeholders throughout the research project—in designing trials, determining objectives and sharing research outcomes with them.[24] Similarly, the Clinical Trials Transformation Initiative (CTTI), an international multidisciplinary membership body for improving clinical trials, has devised recommendations about engaging patient groups in all phases of drug development "from bench to bedside and back".[25]

A range of varying definitions and terminologies

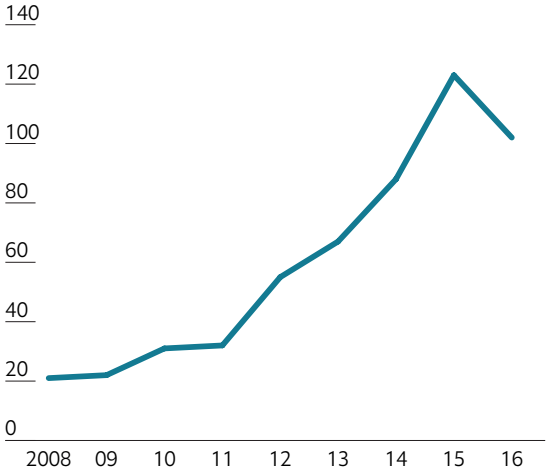
Clinical trials citing patient-centric designs in PubMed have risen since 2008, with a sharp increase since 2011 (Figure 10). When looking at patient-centric clinical trials in PubMed, the number is much lower than when generally searching for these terms in articles, suggesting that there is plenty of editorial comment about patient-centered innovation. But as well as commentary, we found a healthy number of patient-centric trials in Trialtrove® for our analysis (Table 2). Nevertheless, there is no agreed common lexicon or standardized definitions in this area of innovation.

Table 2: Number of patient-centric trials across geographies.

Geographies	No. of patient-centric trials	% of all patient-centric trials
China	108	5
EU	666	34
Japan	168	9
US	761	38
Other geographies	282	14

Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-17. Note that whereas the total number of patient-centric trials in our sample is 1,012, the total listed in this table exceeds that number due to trials taking place across multiple countries.

Figure 10: Number of clinical trials citing patient-centric trial design in PubMed
(No. clinical trials)



Source: PubMed, 2018. Data: 2008-2016.

Thirty-eight percent of patient-centric trials were conducted in the US, 34% in the EU, 9% in Japan and 5% in China. Other geographies made up the remaining 14% (Table 2). Patient-centric trials were most common in oncology in the US, EU, China and Japan, whereas neurology (central nervous system or CNS) was the leading therapy area for patient-centric trials elsewhere (Figure 13).

Patient-centric trials improve likelihood of launch

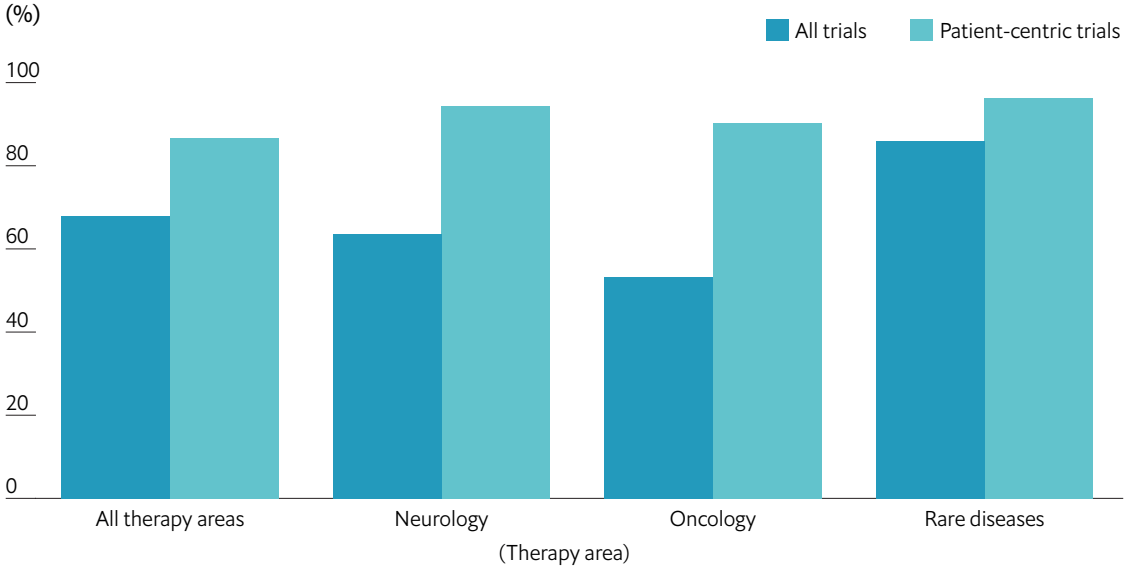
Drugs developed using patient-centric designs were more likely to be launched (by 19 percentage points, at 87%) than drugs developed without such designs (68%; Figure 11). This pattern remained consistent across all three selected therapy areas.

Generally quicker enrollment times, particularly in rare diseases

Patient-centric trials took just four months on average to recruit 100 participants—significantly less than the all-trials average of seven months (Figure 12). The nature of patient-centric trials means that they are probably more effective at engaging patients. The impact at the level of the selected therapy area is even more profound. Patient-centric trials took around half as much time to recruit 100 participants in neurology and oncology trials, and in rare-disease trials they took only a fifth of the time taken by non-patient-centric trials.

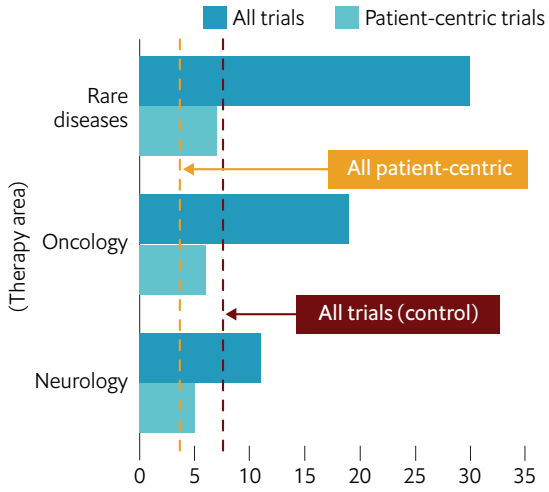
Patient-centric trials in the US, the EU, China and Japan took less time to recruit 100 participants compared to other geographies (2.6 months vs 5.3 months; Figure 15). Trials in the EU took 3.1 months on average to recruit 100 participants, while in China they took just two months. Patient-centric trial enrollment as a percentage of total trial time was shorter in the US, the EU, China and Japan than elsewhere (Figure 14), meaning that the amount of the total trial time spent on treatment could be increased.

Figure 11: Phase II and III likelihood of launch for patient-centric trials vs all trials



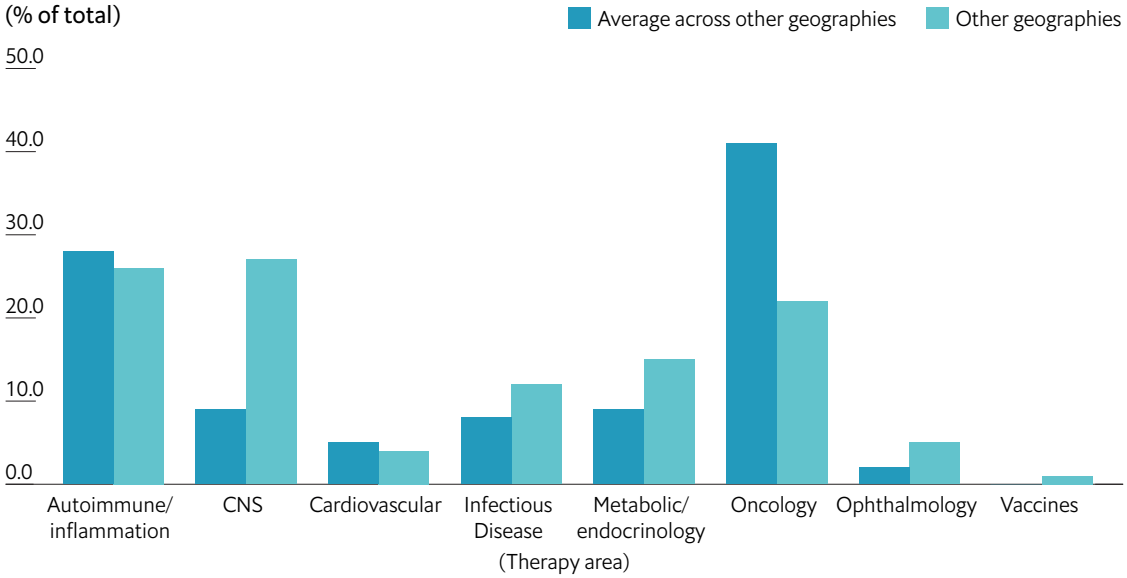
Source: Pharmaprojects® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 12: Average time to enroll 100 participants for patient-centric trials vs all trials



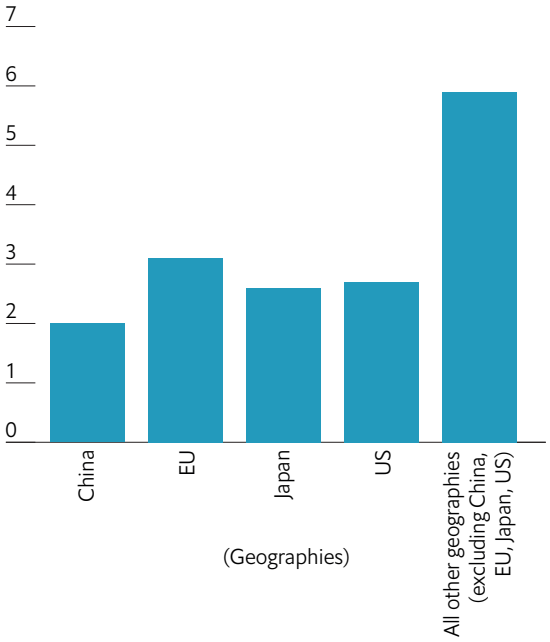
Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Figure 13: Patient-centric trials by therapy area and geography



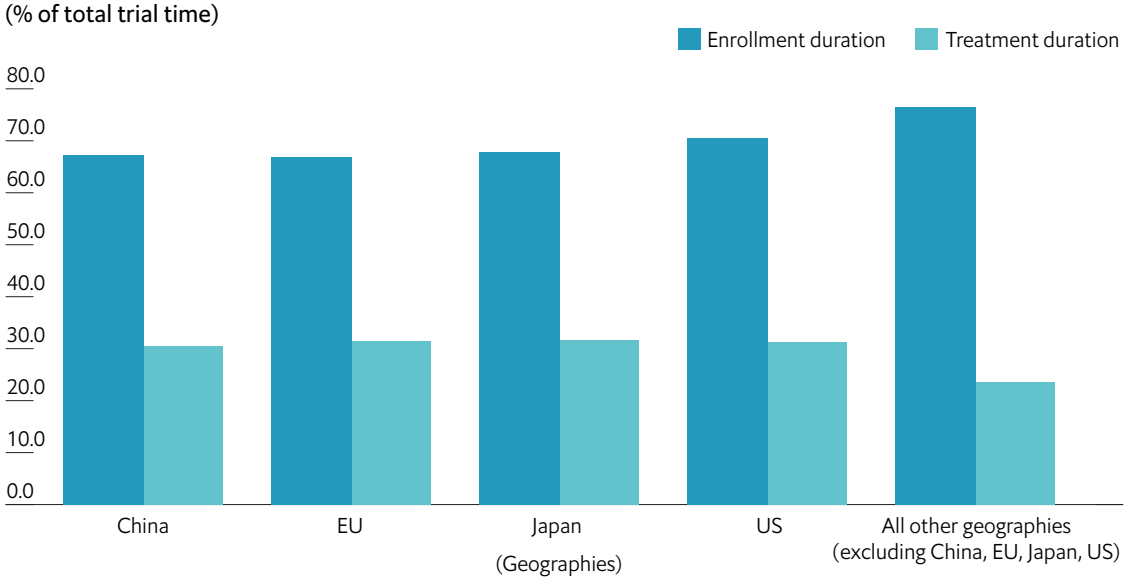
Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 14: Patient-centric trials time to recruit 100 participants



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 15: Patient-centric trial enrollment and treatment duration
(% of total trial time)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

6. Precision medicine trials

"The era of personalized medicine has started…thus the way clinical trials are designed and conducted has to change accordingly. We need to tackle clinical development of every compound as if it was a compound for an orphan disease indication."

Isabelle Naëije, Assoc. Global Trial Director, GDO Trial Management Oncology, Novartis Pharma AG[26]

Precision medicines target known genetic, molecular or cellular markers. They can be tailored to individual characteristics, providing a more personalized approach to treatment. Because precision drugs benefit only those patients who are targeted, it is necessary to use biomarkers to identify suitable patients and predict treatment responses. Thus, precision medicine trials need to weave the use of biomarkers into their design. Precision medicine trials are most common in oncology (for example, tyrosine kinase inhibitors, a class of drugs that can inhibit cancer growth) and some single-gene disorders (such as cystic fibrosis). The potential to stratify and treat patients by disease subtypes often requires modification of traditional trial designs.

The potential value of precision medicines is recognized by major regulators. The EMA, the FDA and the PMDA all encourage the banking of DNA samples during clinical development. The FDA's Biomarker Qualification Program provides a list of approved biomarkers and a streamlined process for their approval.[27] Drug manufacturers can use this information to design trials for inclusion in their regulatory submissions, thus helping to integrate biomarkers into the regulatory review process.

In his 2015 State of the Union address, President Barack Obama launched the Precision Medicine Initiative, now called All of Us. This research program aims to gather genomic data, biological samples and diet/lifestyle information from over a million people in the US, which will be shared on a national research resource platform to advance the field of pharmacogenomics.[28] China has made similar investments in precision medicine, including the field's development as part of the government's Five-Year Plan for 2016-20.[29] The program will aim to gather extensive genomic data in order to understand the prevalence of mutations known to interact with cancer treatments; the focus will be on high-prevalence cancers such as stomach and liver cancer.[30]

Growing in popularity since 2013

The number of precision medicine clinical trials in PubMed has risen sharply in the five years following 2013 (Figure 16). This pattern suggests that the diffusion of precision medicine clinical trials is still in a relatively early phase.

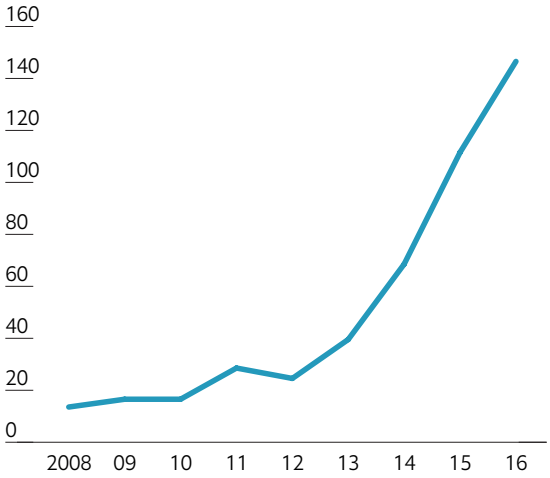
Precision medicine trials are most common in the US (38% of the global total), followed by the EU (34%). Japan and China contribute 11% and 6% of patient-centric trials respectively (Table 3). Oncology is by far the leading therapy area in precision medicine trials; this is unsurprising, as cancer research has been leading the way in precision medicine since its inception (Figure 19).

Table 3: Number of precision medicine trials across geographies

Geographies	No. of precision medicine trials	% of precision medicine trials
China	222	6
EU	1,200	34
Japan	390	11
US	1,318	38
Other geographies	381	11

Source: Trialtrove® | Pharma Intelligence, 2018 Data: 2012-17.
Note that whereas the total number of precision medicine trials in our sample is 2,650, the total listed in this table exceeds that number due to trials taking place across multiple countries.

Figure 16: Number of clinical trials citing precision medicine design in PubMed
(No. clinical trials)



Source: PubMed, 2018. Data: 2008-2016.

Precision medicine trial design improves likelihood of launch across all therapy areas

In line with the trend observed in other innovations, drugs developed using a precision medicine design had a higher likelihood of launch than our all-trials benchmark. This was consistent across all therapy areas (Figure 17). The difference in likelihood of launch was most marked in oncology, where the difference between precision medicine and non-precision medicine was 26 percentage points; this may reflect the fact that precision medicines and precision medicine trial designs in cancer research are more mature than in other therapy areas.

Enrollment time varies across therapy areas

On average, precision medicine trials took longer to recruit 100 participants than the all-trials benchmark (11 months vs 7 months; Figure 18). This may be because precision medicine trials require more detailed screening of potential participants to determine eligibility compared to other types of trials—for example, through the use of genetic or other biomarker testing. However, we found that precision medicine trials were quicker to recruit participants within specific therapy areas. For example, in neurology precision medicine trials took 9.7 months (compared to 10.6 months for controls) and in oncology they took 13.5 months (compared to 18.7 months), while rare diseases saw the largest difference, with 19.1 months for precision medicine trials and 29.7 months for non-precision medicine trials.

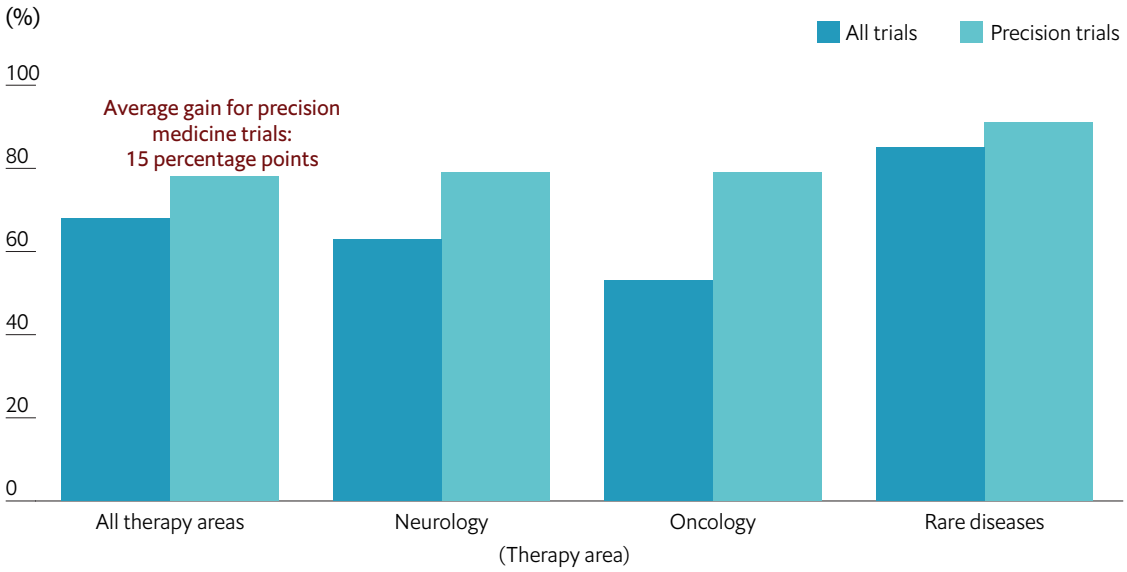
The proportion of total trial time spent on recruitment compared to the treatment phase is similar across all of the innovations investigated in this study. Precision medicine trials had the longest average overall trial duration (41 months), which may be driven by the range of often complex trial designs required in precision medicine.

Trials in the US, the EU, China and Japan took on average a quarter of the time to recruit 100 participants compared with trials in other geographies (7 months vs 28 months). China and Japan had

the shortest times to recruit 100 participants, at five and six months respectively, while trials in the EU and the US took seven and eight months respectively (Figure 21). The very long time to recruit 100 participants (over 25 months) in trials outside of the US, the EU, Japan and China is probably partly due to smaller trial sizes (average accrual number of 95, compared with 339 in the US, 402 in the EU, 408 in Japan and 553 in China).

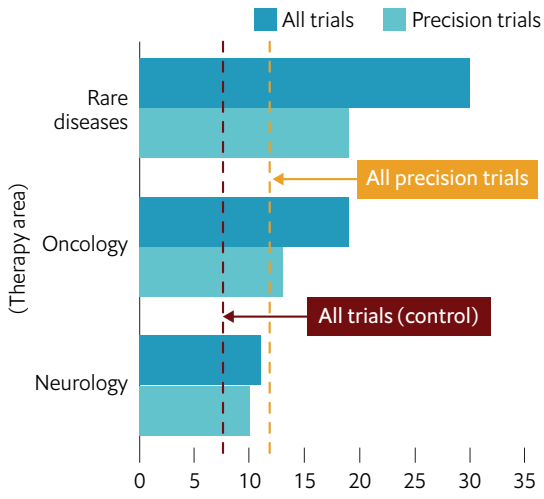
At 66%, precision medicine trials in the US had the lowest proportion of trial time spent on enrollment compared to other geographies, and trials took less time overall in the US than in the EU, Japan or China (Figure 20).

Figure 17: Phase II and III likelihood of launch for precision trials vs all trials



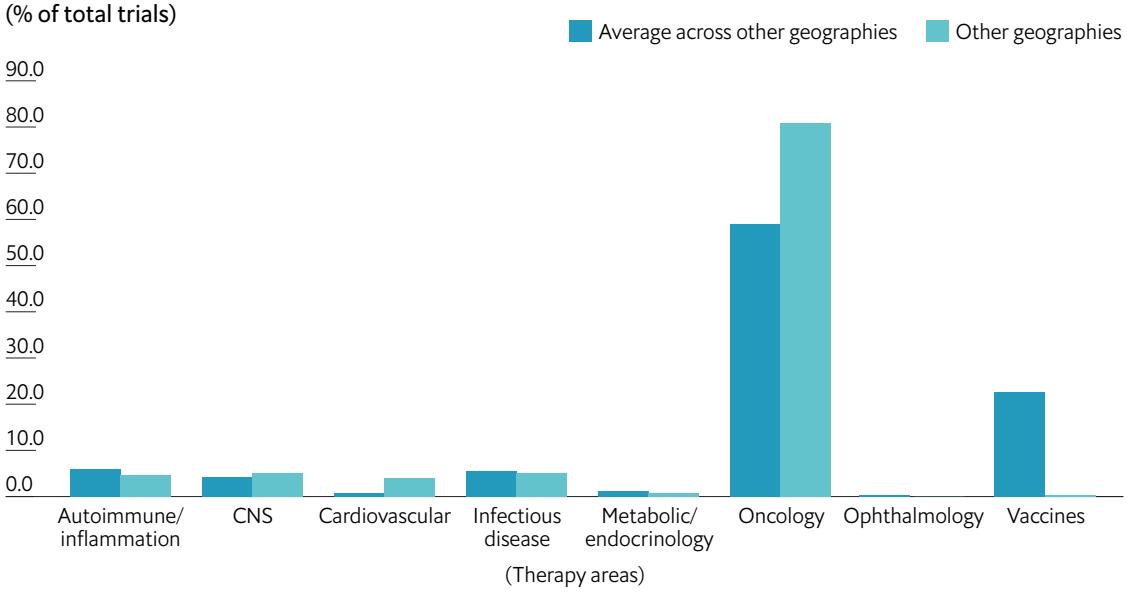
Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Figure 18: Average time to enroll 100 participants for precision trials vs all trials



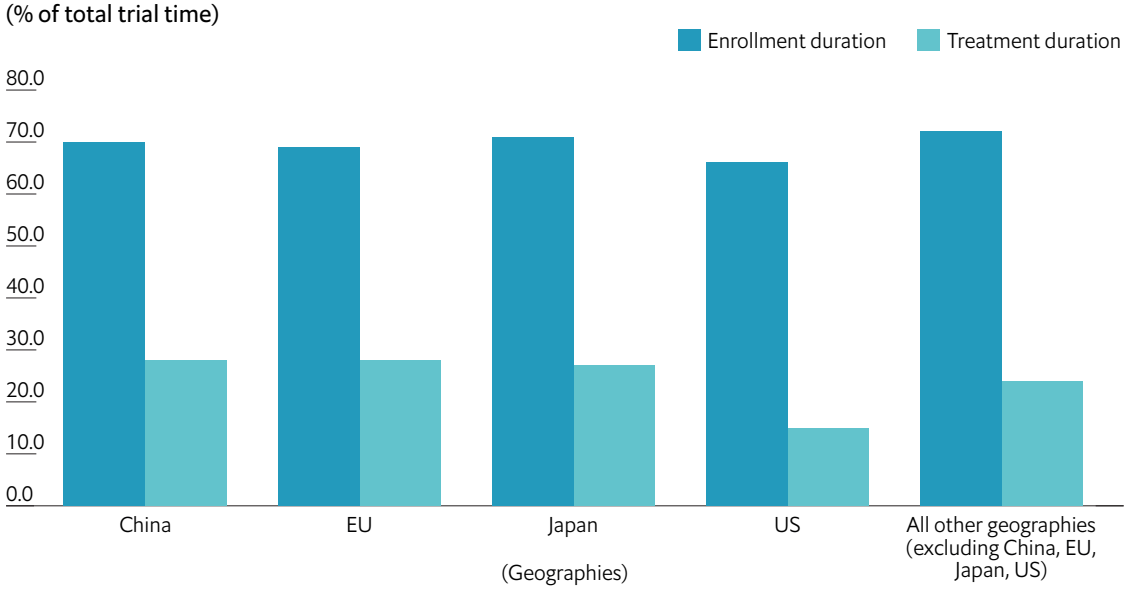
Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Figure 19: Precision medicine trials by therapy area and geography
(% of total trials)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

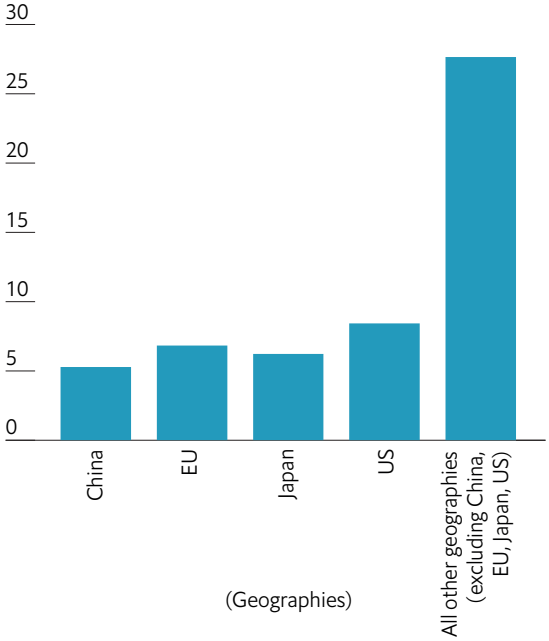
Figure 20: Precision medicine trial enrollment and treatment duration
(% of total trial time)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 21: Precision trials time to recruit 100 participants

(months)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

7. Real-world data trials

"Companies are all collecting RWD just in case; regulators don't yet know what to do with it."

Professor Sir Alasdair Breckenridge, former Chair of the UK Medicines and Healthcare Products Regulatory Agency

Real-world data (RWD) is the term used to describe data collected during drug development and post-marketing approval either to prospectively indicate or to retrospectively measure the impact that a therapy has in a real-world setting, rather than in the trial environment. We use the definition offered by FDA Principal Deputy Commissioner Rachel Sherman and colleagues: "Information [...] from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications."[31] So this can mean recruiting participants via registries, using registry data to create a "virtual" or "historical" control group, or using wearable devices to gather data.

Regulators and reimbursement authorities are increasingly seeking evidence of real-world effectiveness to drive value-based decisions. The evidence base from RWD can support market access by improving discussions with payers, so that drugs not only get approved by regulatory bodies but also make it into the marketplace and on to formularies.

RWD has been embraced by researchers in China, with a rapid increase in the number of disease registries and administrative databases in that country since 2008.[32] In 2015 the CFDA implemented the China Hospital Pharmacovigilance System, which includes electronic medical records from 300 hospitals and healthcare claims data, providing real-world data to complement existing passive drug-safety monitoring by the National Center for Adverse Drug Reactions Monitoring.[32] The Japanese PMDA has also launched a program that supports the development of RWD (among other elements), the "Rational Medicine" Initiative, which is a holistic program designed to make the Japanese health system more patient-centric and evidence-based.[33] The initiative shows a recognition of the importance of RWD by the PMDA and a willingness to invest funds in creating the necessary infrastructure (such as the Medical Information Database Network, or MID-NET).

In August 2017 the US FDA issued guidance on the *Use of real-world evidence to support regulatory decision-making for medical devices*, and it has held public meetings and workshops to discuss the use of RWD in drug development.[34, 35] The EMA in the EU has also embraced the use of RWD. The drug eculizumab was given orphan designation in 2003 for the treatment of paroxysmal nocturnal hemoglobinuria (PNH),[36] and its orphan designation was later extended based on real-world data from the international PNH registry.[37] The Salford lung study complemented trial-based data with data from the electronic medical records of patients on their interactions with general practitioners, pharmacists and hospitals in the "real world".[38, 39] The trial was designed by the drug's manufacturer to be part of its regulatory submission, and involved interaction with the regulators from the outset to maximize its regulatory acceptability as well as its potential for clinical effectiveness.

Use of RWD has increased steadily since 2008, but mainly in post-marketing trials

The number of articles about RWD in PubMed has risen sharply from approximately 8,000 in 2008 to over 20,000 in 2016. A similarly steep rise is seen when looking just at clinical trials across all trial phases (Figure 22).

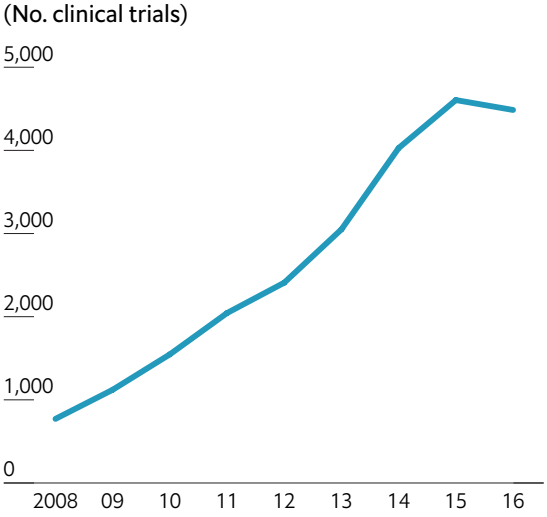
Yet our analysis identified fewer RWD trials in Trialtrove® than for any other innovation. This may be because RWD is currently used primarily in phase IV trials onwards, when drug developers look at safety and effectiveness in real-world use, whereas our Trialtrove® analysis focused on phase II and III trials. The low numbers in Trialtrove® may also reflect the nature of this database, which focuses on interventional studies, so that its coverage of RWD studies (for example, registry studies) may not be as comprehensive as for the other selected innovations.

Table 4: Number of RWD trials across geographies

Geographies	No. of RWD trials	% of RWD trials
China	4	6
EU	24	34
Japan	2	3
US	32	46
Other geographies	8	11

Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 22: Number of clinical trials citing real-world data in PubMed



Source: PubMed, 2018. Data: 2008-2016.

The US (46%) and the EU (34%) contributed most of the RWD trials in our sample, with China and Japan contributing 6% and 3% respectively and the rest of the world 11%. It should be noted that again the numbers here are small, at just 57 trials (Table 4).

While oncology research has been the leading therapy area for our other innovations, in RWD the leading area has been neurology (Figure 25). The neurology classification in Trialtrove® includes therapy areas such as mental health, addiction, pain, multiple sclerosis and Parkinson's disease. These are all areas where it can be challenging to recruit trial participants—this is particularly so in trials with a mental health element, where there is also a high attrition rate during trials—so a RWD approach to collecting data may be valuable.

RWD improves likelihood of launch across all therapy areas

As with all our innovations, drugs developed using RWD had a higher likelihood of launch (89%) than the all-trials comparison group (68%); this pattern was found across all therapy areas. However, given the small number of trials (57), we are unable to make a meaningful assessment of variation across specific therapy areas.

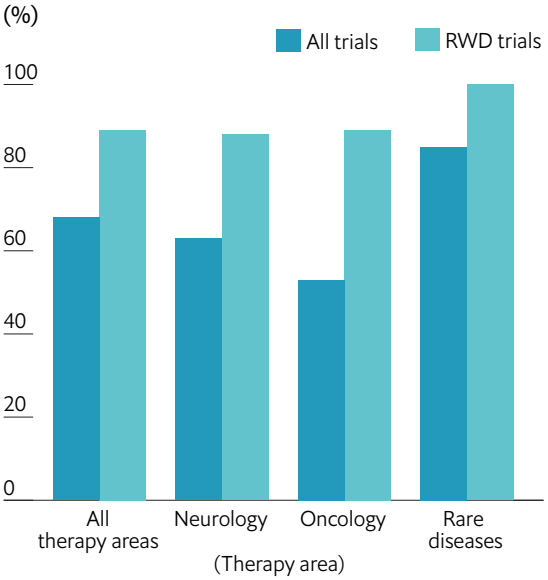
Enrollment time varies across therapy areas

Clinical trials incorporating RWD took on average six months to recruit 100 trial participants, compared to seven months for all trials (Figure 24). Recruitment time was reduced in RWD trials in neurology (9.7 months vs 10.6 months) and rare diseases (26.8 months vs 29.7 months). However, in oncology RWD trials took just over a month longer to recruit 100 participants, at 20.2 months compared to 18.7 months. When trying to explore why RWD oncology trials took longer, the dataset proved too small to allow for further meaningful manipulation of the data, such as removing outliers. Oncology aside, reductions in recruitment time may be due to procedural efficiencies. For example, RWD trials may use registry data to form part of their study cohort or may use electronic health records to identify participants.

Time to recruit 100 participants appears to be much lower in the US, the EU, China and Japan than elsewhere, at an average of seven months compared to 59 months (Figure 27). Again, we must be cautious in our interpretation of this result, as there are only eight RWD trials outside of the selected geographies.

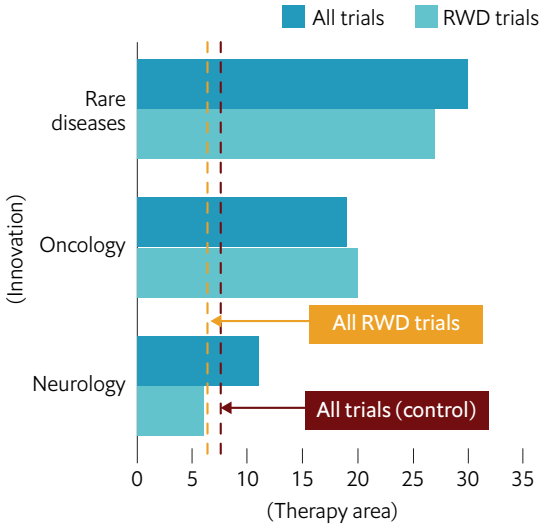
Figure 26 suggests that the average enrollment time for RWD trials in other geographies is 100% of total trial duration, despite an average 16% of time attributed to treatment. This is due to the fact that the underlying data contain a mixture of actual data and estimates for the length of trials, accrual duration and treatment duration. The presence of estimated data means that there is a margin of error in these calculations.

Figure 23: Phase II and III likelihood of launch



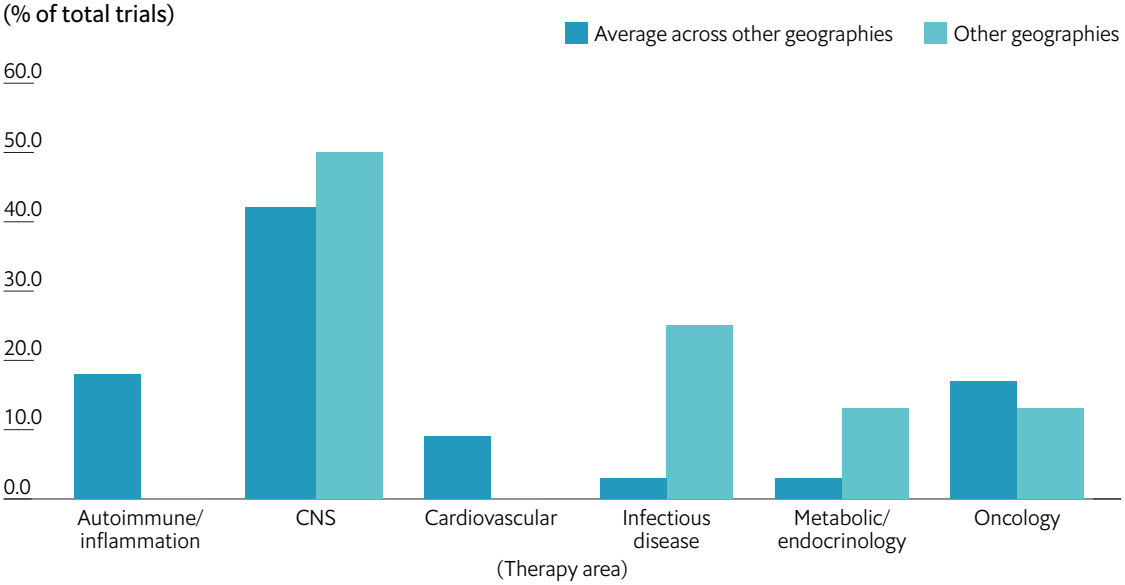
Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 24: Average time to enroll 100 participants for RWD trials vs all trials



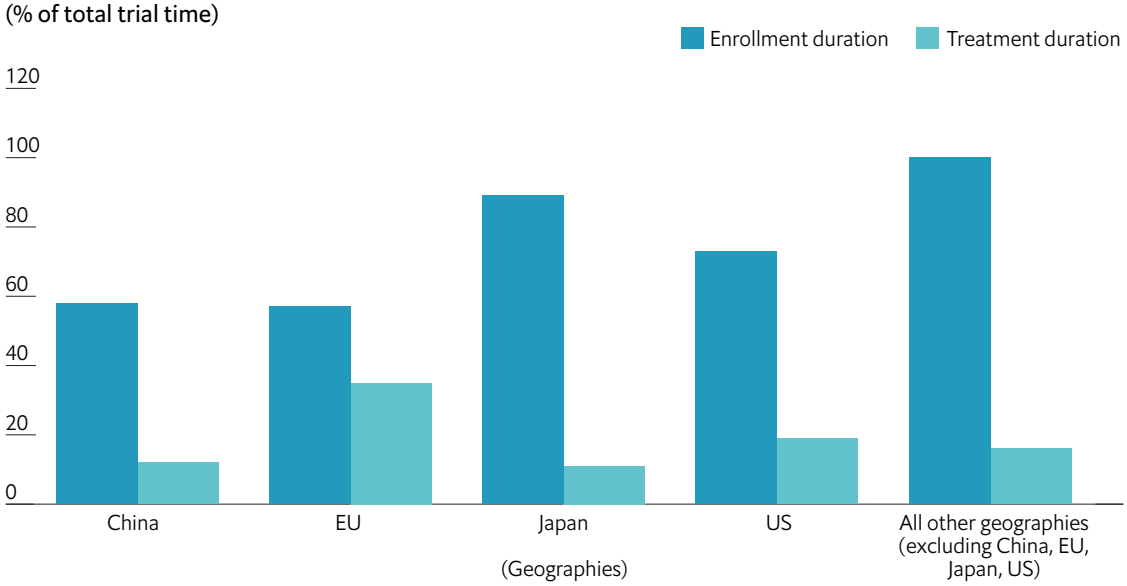
Source: Trialtrove® | Pharmaintelligence, 2018. Data: 2012-2017.

Figure 25: RWD trial therapy areas by geography



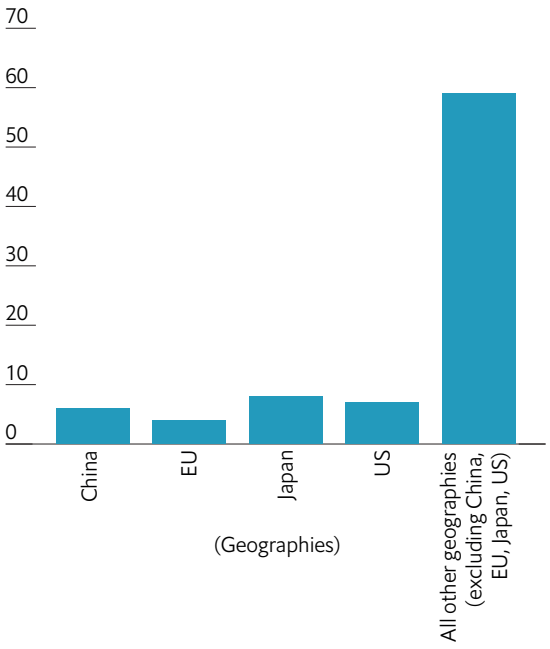
Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 26: RWD trial enrollment and treatment duration
(% of total trial time)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 27: RWD trials time to recruit 100 participants
(months)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

8. Findings by therapy area

Rare diseases has the highest proportion of innovative trials

Looking across all innovation types, rare diseases had the largest proportion of innovative trials (26%) of total trials) among the therapy areas (Figure 29). This result was driven by the large number of precision medicine trials that took place within rare diseases. Perhaps surprisingly, given its reputation as a leader in innovation, oncology had the smallest proportion of innovative trials, at just 6%, although oncology has by far the largest number of adaptive trials. The proportion of innovative trials in neurology was smaller than in rare diseases but larger than in oncology, although there were several RWD trials in this area.

The greatest benefit to likelihood of launch is seen in oncology

Drugs developed using the selected innovations (adaptive, patient-centric, precision medicine and RWD trials) all had a higher likelihood of launch than drugs developed using non-innovative trials. This pattern was consistent across all three selected therapy areas (neurology, oncology and rare diseases). The greatest benefit was delivered in cancer research, where use of the selected innovations improved the likelihood of launch by 33 percentage points, from 53% to 86% (Figure 30). In neurology, improvement in likelihood of launch was 23 percentage points, while in rare diseases it was 3 percentage points. Averaging these results out across all three selected therapy areas, innovation added a healthy 16 percentage points to likelihood of launch.

The narrow margin of improvement in rare diseases may reflect the business model for drug development in this area, which concentrates on developing relatively few drugs which, however, generally have a higher likelihood of success. At the other end of the spectrum, the large innovation benefits that seem to accrue to oncology drugs is frustrating, as it suggests that the therapy area that benefits the most from innovative trial designs appears to be using them the least as a proportion of the total number of trials conducted.

Patient-centric trials offer rapid enrollment times, particularly in rare diseases

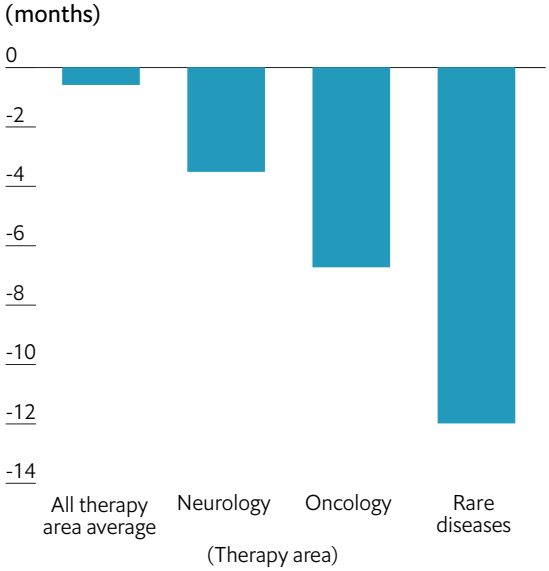
Innovative trials were quicker to enroll 100 participants than non-innovative trials (six months vs seven months). However, there was significant variation across therapy areas. In neurology, innovative trials took seven months to recruit 100 participants, compared to 11 months for non-innovative trials. In oncology, innovative trials took 12 months, whereas non-innovative trials took 19 months. The difference was greatest in rare diseases, where innovative trials took 18 months, compared to 30 months for non-innovative trials (Figure 30).

This last figure is driven mainly by the large number of patient-centric trials in rare diseases. Patient-centric trials had a short average time to enroll 100 participants—three months less than non-innovative trials (Figure 12). In neurology and oncology, recruitment to patient-centric trials took only half the time of recruitment in non-innovative trials and just a fifth of the time for patient-centric trials in rare disease.

Innovative trials are enrolling more people in a shorter time

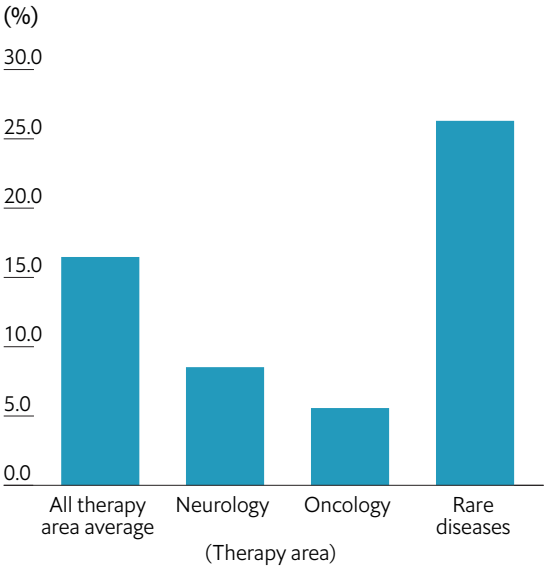
There were consistent differences in the average actual accrual numbers (that is, the numbers of people recruited to trials) between innovative and non-innovative trials. Across all three selected therapy areas, non-innovative trials generally recruited 85 fewer participants per trial (Figure 30). Innovative neurology trials recruited an average 164 more people into trials, while oncology trials recruited 123 more participants and rare disease trials recruited 132 more. This means that, despite the fact that innovative trials tend to be larger, patients can often be enrolled into them in the same amount of time or less than that needed to enroll into non-innovative trial.

Figure 28: Difference in time to recruit 100 participants between innovation and non-innovation trials



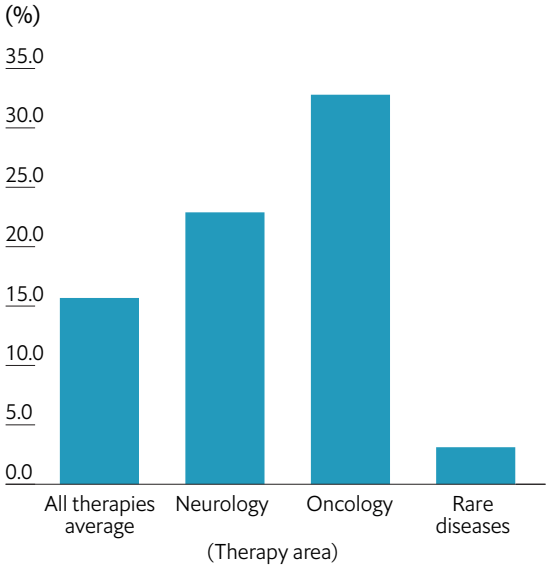
Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 29: Innovative trials as a percentage of total trials



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

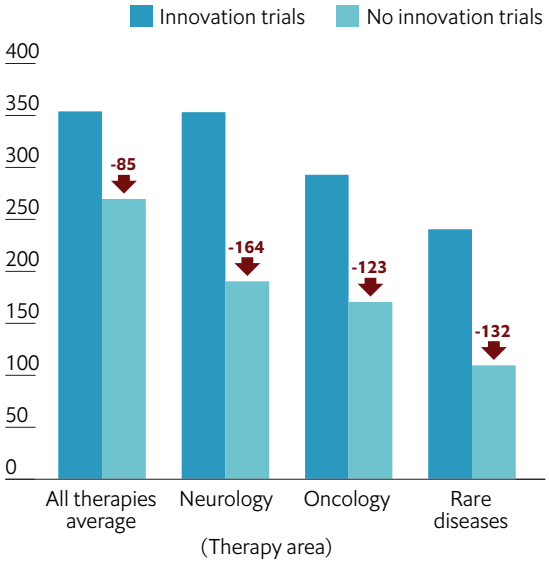
Figure 30: Increase in likelihood of launch for innovative drugs compared with non-innovative drugs



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

Figure 31: Average actual accrual number

(No. of patients)



Source: Trialtrove® | Pharma Intelligence, 2018. Data: 2012-2017.

9. Market access

The last metric of success that we tested had to do with the ability of new drugs to be added onto payer formularies or other national approved-drug lists. This metric is used as a proxy for patient access. It is posited that, while regulatory bodies may be accepting of new and innovative trial designs, payers and providers may be less ready to accept evidence from such trials. They may therefore ask for more evidence before adding drugs to their formularies or reimbursement lists, hence slowing down access to these drugs (even if they have moved through the regulatory process more efficiently).

Formularies across the US, the UK and Japan show rapid adoption of drugs developed using innovative trials

To investigate access, we looked at how many new molecular entities (NMEs) that gained regulatory approval in 2015-17 and were developed using one or more of the innovations had achieved formulary addition by 2018. We compared these with drugs that were developed without using any of the four innovations described (Table 5).

The formularies studied consisted of six in the US, the British National Formulary in the UK and the National Health Insurance Drug List in Japan (see Table 5). For regulatory approval, we looked at the FDA in the US, the EMA for the EU and the PMDA in Japan. While we were able to locate a recent list of reimbursed "Western medicines" in China, no list of drugs recently approved by the CFDA was available. We therefore looked at how many drugs recently approved by the US FDA were available on the Chinese list of reimbursed medicines, and found that just one, Corlanor (ivabradine), was listed. We were therefore unable to conduct the innovative vs non-innovative analysis for China.

As detailed in Table 5, among those formularies reviewed, drugs developed using innovative methods generally make their way on to the lists quicker. We acknowledge that while formulary addition is an important step towards patient access, other factors, such as price, will realistically affect patient access. For example, although most drugs developed using innovative trial designs are listed, that does not necessarily mean seamless access; for example, most of the drugs reviewed required "prior authorization" in US formularies, and many were high-tiered and/or listed as "non-preferred," meaning that higher co-pays would be required. Nevertheless, there emerges evidence of a trend of earlier listing for drugs developed using innovative trials.

National regulation and pharmacy access data in Europe show a similar pattern of early adoption

Since national formularies or national lists of reimbursed drugs are not publicly available in most European countries, to complement our formulary analysis we also looked at drugs' presence or absence on the following databases in Germany, Sweden, Italy and Spain:

- **Germany** (AMIS, German Drug Information System): Lists drugs currently approved by German regulatory authorities. AMIS contains the approval data of the German drug regulatory authorities BfArM (Federal Institute for Drugs and Medical Devices), PEI (Paul-Ehrlich-Institut—Federal Institute for Vaccines and Biomedicines) and BVL (Federal Agency for Consumer Protection and Food Safety).
- **Sweden** (Fass): Lists drugs currently available at Swedish pharmacies. Fass is produced by Läkemedelsindustriföreningen Service AB (LIF), which is the industry organization for research pharmaceutical companies operating in Sweden. LIF represents about 80 companies, which account for about 80% of all medicines sold in Sweden. Members of Fass include, for example, generic companies, parallel importers and natural-medicine companies, totaling more than 200 companies. The companies participating in the collaboration are responsible for their product texts on Fass and continuously update them.
- **Italy** (AIC): Lists drugs currently approved by Italian regulatory authorities. The marketing authorization (AIC) is the provision by which the Italian Medicines Agency (AIFA) certifies that a given medicinal product can be marketed in Italy. The AIC is granted by AIFA after a group of experts has assessed the quality, safety and efficacy of the product.
- **Spain** (CIMA): Lists drugs authorized by Spanish regulatory authorities. Displayed information makes reference to a medicine's availability in community services and/or pharmacy services, as well as details of the authorization and marketing status and possible supply problems.

These lists do not map directly on to formulary addition or payer reimbursement, but they do reflect a stage on the journey towards patient access. Table 6 shows a similar pattern to that seen in Table 5—namely, that drugs developed using innovative trials are generally more likely to be listed than drugs not developed innovatively.

Importantly, we found no evidence of any delays in listing innovative drugs on the analyzed formularies or national drug lists. Figure 32 uses the data from Table 5 and Table 6 to show the proportion of drugs developed using innovative trials (vertical axis) against the proportion of drugs developed without innovative processes (horizontal axis) for each formulary/national list, for the years 2015, 2016 and 2017. On a proportional basis, more innovative drugs are present on every formulary and on every reimbursement, regulation or pharmacy access list in every year. There are three exceptions to this trend: in 2017, the Italian AIFA drug database listed more non-innovative than innovative drugs, as did the PMDA in Japan in 2015, while in 2015 Germany's AMIS listed the same proportion of innovative and non-innovative drugs.

Figure 32: Proportion of recently approved drugs (a) developed with innovations and (b) developed without innovations on formularies or other national lists of market access
(%)

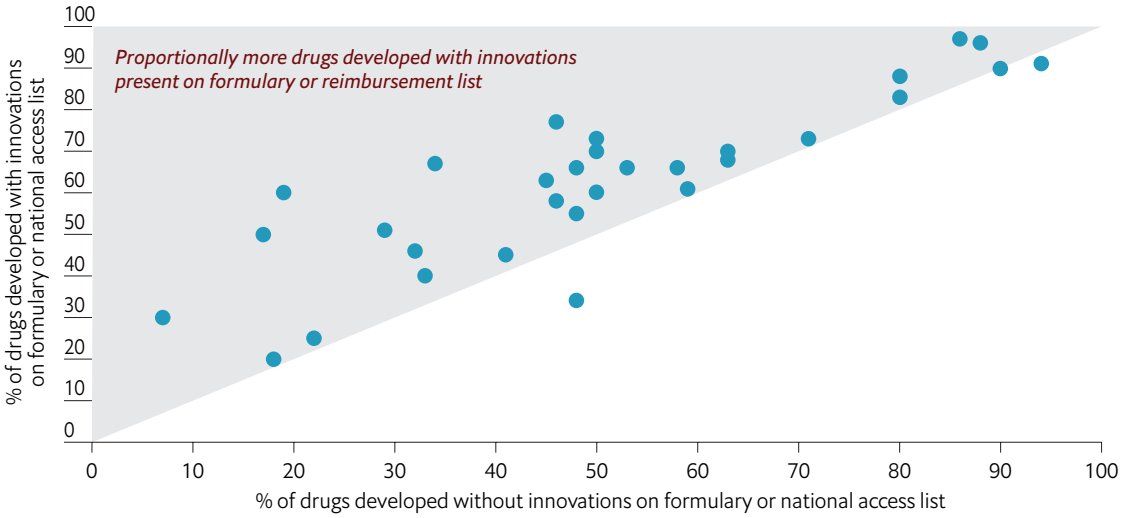


Table 5: Comparison of formulary or reimbursement list approval for drugs developed with and without innovations

	Year of regulatory approval	2015			2016			2017		
Geography & entity	Formulary or national regulatory approval	No innovations	With innovations	**Percentage point change with innovation**	No innovations	With innovations	**Percentage point change with innovation**	No innovations	With innovations	**Percentage point change with innovation**
US: FDA	SilverScript list of covered drugs (Medicare)	38%	50%	**+12**	33%	40%	**+7**	22%	25%	**+3**
	United Healthcare, Community plan (Medicare)	46%	77%	**+31**	50%	60%	**+10**	7%	30%	**+23**
	Blue Cross Blue Shield Clinical drug list	71%	73%	**+2**	50%	60%	**+10**	48%	55%	**+8**
	Aetna Premier Plan	71%	73%	**+2**	50%	70%	**+20**	41%	45%	**+4**
	Cigna Comprehensive drug list	50%	73%	**+23**	17%	50%	**+33**	19%	60%	**+41**
	Humana HDHP traditional drug list	63%	68%	**+5**	50%	70%	**+20**	63%	70%	**+7**
EU: EMA	NHS British National Formulary	58%	66%	**+8**	45%	63%	**+18**	29%	51%	**+22**
Japan: PMDA	National Health Insurance Drug List	94%	91%	**-3**	86%	97%	**+11**	59%	61%	**+2**

Table 6: Comparison of national regulatory approval or other listing of drugs developed with and without innovations

	Year of regulatory approval	2015			2016			2017		
Geography & entity	Formulary or national regulatory approval	Non-innovation	Innovations present	**Percentage point change with innovation**	Non-innovation	Innovations present	**Percentage point change with innovation**	Non-innovation	Innovations present	**Percentage point change with innovation**
EU: EMA	Germany: AMIS (German Drug Information System)	90%	90%	**0**	88%	96%	**+8**	86%	97%	**+11**
	Sweden: Fass database	53%	66%	**+13**	46%	58%	**+12**	32%	46%	**+14**
	Italy: AIFA drug database	80%	83%	**+3**	80%	88%	**+8**	48%	34%	**-14**
	Spain: Online Medicines Information Center of AEMPS (Spanish Medicines Agency)	48%	66%	**+18**	34%	67%	**+33**	18%	20%	**+2**

10. Discussion and conclusions

The results presented in this report clearly demonstrate that the right innovations can and do have an impact on drug development and market access. All four innovations studied—adaptive, patient-centric, precision medicine and real-world data (RWD) trials—have positive impacts on trial time, recruitment and market access. Enrollment time was generally improved across nearly all instances of innovation compared to the non-innovation control, although other factors—including average accrual numbers—also had an impact. It is natural to expect that smaller trials would take longer on average to recruit participants, as larger trials benefit from economies of scale. Similarly, it is unsurprising that rare diseases took the longest time to recruit, as eligible patients are relatively scarce. Nevertheless, all three therapy areas saw substantial improvements in enrollment times.

Improvements in likelihood of launch and in patient access were likely driven by the advantages inherent in the innovations themselves. For example, adaptive trials are flexible enough to use a range of dosages within a robust design, and often use genotyping and biomarkers (a type of precision medicine technology) to identify specific patient groups that may benefit. RWD can likewise offer a more nuanced understanding of who will benefit from a therapy and why. Meanwhile, patient-centric trials may be more appealing to participate in because they offer more relevant benefits to patients than those developed in a less patient-centric manner. The emerging trend that we see—of payers being more likely to add drugs developed using some kind of innovation to their formularies—may reflect that. Trials using innovations therefore offer greater opportunities to produce drugs that meet patient, regulator and payer needs.

Innovations may also support post-approval stages. For instance, although randomized control trials (RCTs) remain ideal for determining the efficacy and safety of new treatments, they are sometimes insufficient to address the evidence requirements of regulators and payers, which may prefer RWD.[40] Such data can be incorporated into RCTs through hybrid trials that collect data on safety and effectiveness as well as on implementation.[41] Another approach is to incorporate RWD as an add-on to RCT data supporting product approval, but with an increasingly important role in informing reimbursement decisions and accelerating the acceptance of drugs on to formularies.[42] This holds promise for expediting the last step of the pathway: granting patients access to the treatments they need, when needed.

Taken together, the data make a compelling case for enabling the adoption of new innovations and technologies in drug development and market access. No one innovation is a silver bullet, but this tool kit of effective innovations offers a valuable opportunity for the industry to improve productivity.

Limitations of this study

We acknowledge some important limitations to our study. First, our analysis included more patient-centric and precision medicine trials than adaptive or RWD trials. Therefore, when results presented around innovation as a whole versus non-innovation, they mainly reflect precision medicine and/or patient-centric trials. Secondly, we used the functionality of Trialtrove® and Pharmaprojects® (both

Citeline® tools) to follow drugs during their phase II and III trial stages through to their eventual launch. While Citeline® is an industry standard for the collection of clinical trials and drug development pipelines, no source is ever fully comprehensive. However, we are confident that the tools we used to identify trial data, outcomes, and launch data provided a fair representation of global trends. Third, our analysis of market access looked at a combination of formularies, reimbursement lists, national regulatory approval and pharmacy access. All of these taken together are proxies for the final step of getting drugs to people who need them in a timely and affordable manner; usage or prescription data, where available, could complement this analysis. Finally, we could have selected other innovations, and the original longlist of areas to investigate was whittled down by the expert panel. Nevertheless, the innovations we looked at are themselves umbrella terms, that encompass a variety of related innovations. We are confident that our results demonstrate that such innovative trial designs can and do improve the efficiency and effectiveness of drug development and market access. However, there is still a need for future work to build on this analysis to provide an understanding of the strengths and weaknesses of individual innovation types and their application at different phases in the pipeline.

The results suggest that the pharmaceutical industry has the tools at hand to improve efficiency and restore sustainability

There is still some way to go for these and other innovations to be able to make substantial impacts and place the pharmaceutical industry on a sustainable footing. Why, for example, given the advantages offered by adaptive and RWD trials, are such trials not more commonly used? Adaptive trials, in particular, have been around for some time and are widely discussed in the literature, but as a proportion of all clinical trials their use remains stubbornly low. It appears that the industry has at its fingertips the tools to improve the drug development and market access process, but in most cases is failing to use them. We explore why this might be the case in our companion report, Barriers, Enablers and Calls to Action.

11. Appendix: Additional information on methodology

The EIU adopted a staged approach, designed to blend quantitative data and qualitative perspectives to frame, validate, investigate and review the material.

The expert panel

The expert panel was central to the entire research project. It was composed of handpicked experts representing pharmaceutical companies, researchers, payers, professional bodies and the technology industry.

The expert panel:

- Dr Roy Auty—Associate Director, Pipeline & Portfolio Planning, Genentech
- Dr Lynda Chin—Associate Vice Chancellor of Healthcare Transformation; Chief Innovation Officer for Health Affairs; Director, Institute for Health Transformation, The University of Texas System
- Dr David Epstein—former Medical Director of a large national health plan
- Dr Alberto Grignolo—Corporate Vice President, PAREXEL
- Mr Jim Kremidas—Executive Director, Association of Clinical Research Professionals
- Dr Rebecca Miksad—Senior Medical Director, Flatiron Health
- Dr Tina Moen—Deputy Chief Health Officer, IBM Watson
- Mr Bernard Munos—Senior Fellow, FasterCures; Founder, Innothink Center for Research in Biomedical Innovation

Key Definitions

The four innovations that were prioritized during the panel discussion in more detail:

- Adaptive trial designs: these trials incorporate pre-specified modifications into the protocol, allowing for changes once the trial is in progress based on interim data analysis. Adaptive trials can modify the sample size or dosing, test the same drug in multiple conditions with a common genetic mutation (basket trials), test multiple treatments for the same condition (umbrella trials) or separate trial phases with interim data analyses (seamless trials).
- Patient-centric trials: these trials consider and/or include patients in trial design and execution, for example involving patients in trial design to ensure that trial outcomes are relevant to patients and that participation is as convenient as possible.

- Precision medicine trials: these are trials of medicines that target specific genetic, molecular or cellular markers. Trials can include a diagnostic test, through the use of biomarkers, to identify the patient with the target. These and other new approaches required in precision medicine have led to innovation in the design of trials.
- Real-world data (RWD) trials: these trials measure the impact that a therapy has in real-world settings, rather than in the trial environment. This can mean recruiting participants via registries, using registry data to create a "virtual" or "historical" control group, or using wearable devices to gather data.

The three selected therapy areas prioritized during the panel discussion in more detail:

- Neurology: an area where demand is projected to grow, as the incidence of conditions (such as dementia) for which there are few effective treatments continues to increase.
- Oncology: often leading the field in many aspects of innovation, cancer research represents a rapidly growing population of patients and associated needs.
- Rare diseases: these diseases often struggle with a high level of unmet need in a small global patient population.

Identifying sources for the research

The EIU used Citeline® as its primary source—specifically its databases Trialtrove® for data from clinical trials and Pharmaprojects® for data on likelihood of launch.

Trialtrove® collects data from 40,000 sources, including international trial registries such as clinicaltrials.gov, industry press releases and analyst insights, to provide actual and estimated data. It further breaks down data on trials times to enable a deeper analysis of accrual times, treatment times and total trial times.

Because this study examined the impact of innovations on trial times and likelihood of launch, Citeline®'s ability to link through from trials using these innovations in Trialtrove® to the actual developed drugs that used these trials in Pharmaprojects® was a key functionality. This provided the data needed to calculate likelihood of launch.

Identifying trials and drugs for analysis

To identify trials relevant to our innovations we searched the database Trialtrove®, which contains trial data such as therapy area, trial locations, recruitment time, treatment time and overall trial time.

Where possible, we used Trialtrove®'s built-in keywords assigned by their analysts to identify trials completed between December 31, 2012 and December 31, 2017, as this is the most precise way to identify relevant trials. Where built-in keywords were not available, we used search terms identified while reviewing the findings of the literature review to search through the different fields of data in Trialtrove®.

Innovation	Search terms	Trialtrove® keywords	Number of trials
Adaptive		adaptive OR basket OR umbrella	107
Patient-centric	"patient centered" OR "patient-centered" OR "patient centric" OR "patient-centric" OR "patient friendly" OR "patient-friendly" OR "patient input" OR "patient-input" OR "patient reported" OR "patient-reported"		1,012
Precision medicine		PGX - Patient Preselection/Stratification† OR PGX - Biomarker Identification/Evaluation††	2,650
Real-world data	"real world" OR "real-world" OR "electronic health" OR "ehr" OR "claims data*" OR "billing data" OR "registry" OR "registries" OR "outpatient" OR "out-patient" OR "in home" OR "health monitoring" OR "health-monitoring"		57

† PGX - Patient Preselection/Stratification—this keyword is applied to trials that use pharmacogenomics and pharmacogenetics analysis for patient selection or stratification.

†† PGX - Biomarker Identification/Evaluation—this keyword is applied to pharmacogenetics trials that aim to identify or evaluate novel genomic biomarkers to predict response to therapy or toxicity.

To identify trials in the selected therapy areas, we combined these search strategies with Trialtrove®'s built-in filters for the therapy areas of neurology (central nervous system or CNS) and oncology. For rare diseases we selected the most common rare diseases listed by the European Council and covered by Trialtrove®'s disease filters: cystic fibrosis, Huntingdon's, multiple myeloma, retinitis pigmentosa and sclerodoma.[43]

When comparing the results of our searches in Trialtrove® to searches undertaken in PubMed, we see that there were fewer trials in Trialtrove® than PubMed. The main reason for this is that the PubMed searches were limited to clinical trials but were not limited by trial phase, whereas searches in Trialtrove® were limited to phase II and III trials. The difference in search results was particularly marked in adaptive and RWD trials. This may be because of variations in how these trials are described, although our search strategies were designed to be sensitive in order to try to retrieve relevant studies. Limiting by trial phase would have affected RWD trials in particular, because the majority of these trials are phase IV post-marketing studies. The difference may also be attributable to database coverage: Trialtrove® tends to focus on interventional studies, whereas RWD trials are often observational in nature.

To identify a comparator set of trials or "benchmark", we searched Trialtrove® for all phase II and III trials completed between December 31, 2012 and December 31, 2017, and then re-ran the searches for the specific therapy areas to create a control set of trials for each therapy area. This created a control dataset of 19,403 trials across all selected therapy areas.

Calculating likelihood of launch using Pharmaprojects®

After searching in Trialtrove® using the above search strategies, we selected the option to "View Drugs" in Pharmaprojects® in order to identify the drugs developed using these innovations in the retrieved trials. This process was replicated across therapy areas and for the control datasets. Pharmaprojects® provides information about drugs including whether they have been launched, discontinued, suspended or no development has been reported.

To calculate likelihood of launch for phase II and III we used similar methods to those used by Thomas et al. The key difference between our approach and that of Thomas et al is that our dataset combined phase II and III rather than looking at likelihood of launch for each trial phase. Our analysis uses the term "likelihood of launch" rather than "likelihood of approval" to reflect the fact that we used the global status of drugs provided by Pharmaprojects® for our calculations, rather than looking for approvals by individual regulators for each drug. This pragmatic decision was taken based on the size of the sample of drugs for analysis.[4] For each set of drugs we counted the number of drugs that were launched, divided by the sum of all drugs launched, discontinued, suspended or that had reported no development. This approach is based on Thomas et al's method of dividing the number of drugs approved by the sum of the number of drugs approved and in development. We compiled sets of drugs for each innovation area, which could also be subdivided by therapy area.

Drill-downs—therapy area and country analysis

Subgroup analyses explored differences in our key metrics between different therapy areas and countries included in the study. The subgroup analyses involved dividing our Trialtrove® datasets by therapy area and country. In the case of therapy area, these were not always mutually exclusive, as trials (and especially adaptive trials) can look at indications across different therapy areas. Similarly with geographies, trials can be multi-center and multi-country trials. The analyses for the selected geographies are not mutually exclusive, because the size of the selected countries/regions meant that making the dataset mutually exclusive would have removed many important multi-center trials. For trials from "other" geographies, we ensured that these were mutually exclusive from the selected geographies to avoid double-counting those studies and conflating the results across the regions.

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