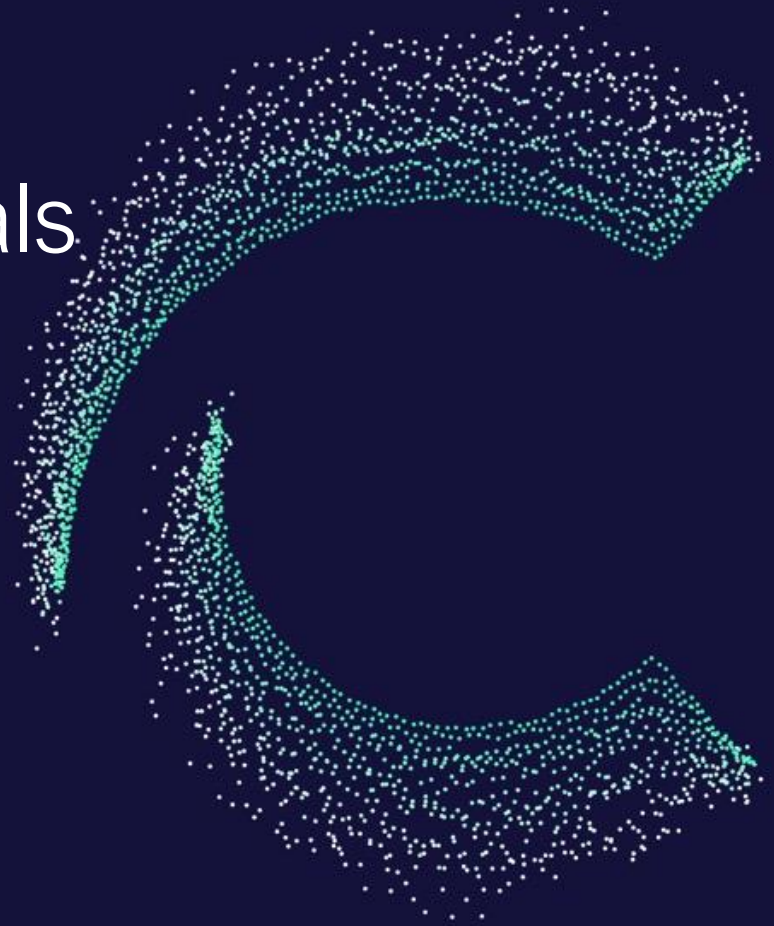
CITELINE

The Netherlands Positioning Within the European Clinical Trials Ecosystem



Created by Citeline Custom Intelligence

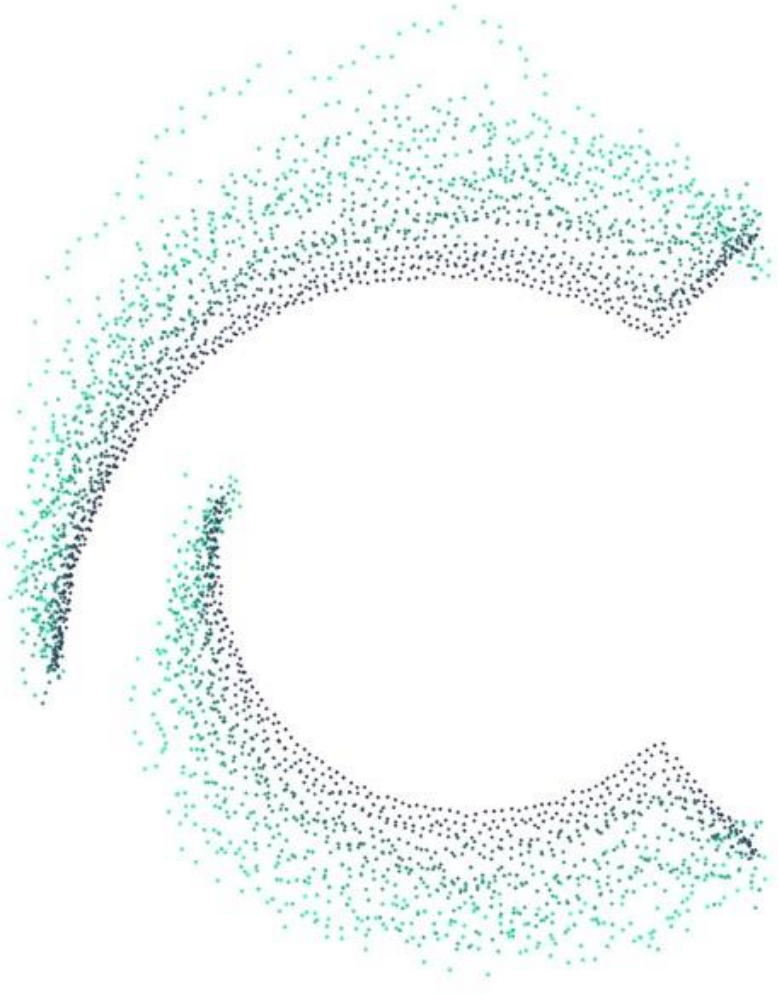
29th August 2023
1st October 2023 (update)

CITELINE.COM

ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

CITELINE

Benchmarking the Netherlands' attractiveness as a top destination for clinical research and looking at how the Netherlands can establish a strong positioning within Europe to be the preferred choice for sponsors conducting clinical trials.

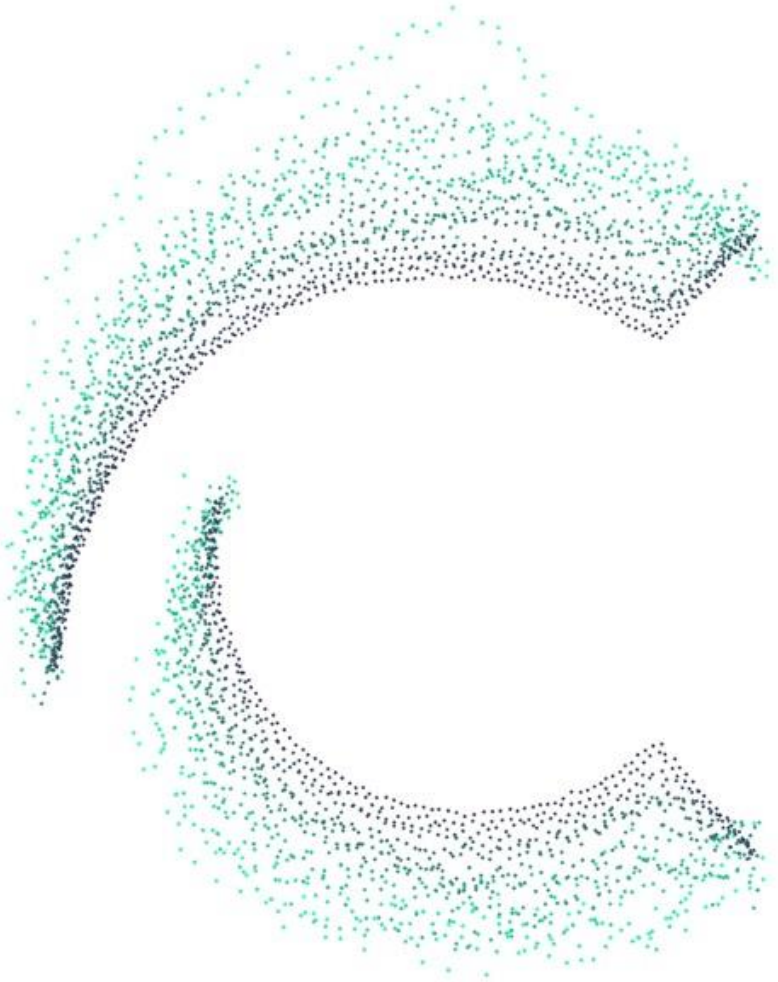


ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Table of Contents

CITELINE

1. Executive summary



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Executive Summary (1/2)

The Netherlands leads in clinical research due to its efficient trial logistics, strong oncology performance, Innovation Leader status, rapid ATMP approvals, and robust infrastructure, establishing it as a global leader

Ongoing studies, participant counts and financial metrics

- Smaller countries outperform larger ones in clinical trials per capita, with the Netherlands initiating 2.9 times more trials per capita than Germany
- Within the Netherlands, oncology trials constitute a significant proportion (33%), followed by autoimmune/inflammation and CNS trials
- The Netherlands offers relatively low-priced comprehensive scientific advice compared to Belgium, Germany and the EMA but ranks second most expensive for basic advice

Academic excellence

- The Netherlands stands out as the 3rd in Europe and 7th globally for Highly Cited Researchers in 2022, claiming 2.9% of the world share
- 100% of the Netherlands' top 10 institutes for clinical, preclinical & health research and all 7 assessed life science research institutes secure positions in the European top 100
- The Netherlands is an Innovation Leader, surpassing the innovation average score by 129%, and excels in the categories of highly cited scientific papers and research systems

Ease of conducting trials

- The Netherlands demonstrates competitive clinical trial start-up times, with the time between trial application and the first patient dosed comparable to Germany and the UK, and stands out in approvals for ATMP trials, one of just two countries to accomplish this in under 30 days, alongside the UK
- With 41 doctors per 10,000 people (close behind Germany and Denmark), the Netherlands' high doctor-to-patient ratio facilitates clinical trial logistics

Availability of patients

- Having the highest population density in Europe (518 people per sq km) and a high hospital density (1.1 hospitals within 5km), the Netherlands offers easy access to a substantial pool of potential clinical trial participants
- The Netherlands leads in patients treated per 100,000 of the population in oncology trials (13.9) and ranks 3rd in metabolic/endocrinology trials
- The Netherlands also leads in the number of rare disease biobanks per 100,000 of the population (0.18)

Executive Summary (2/2)

To improve, the Netherlands should actively engage at international conferences, invest in skilled talent, streamline approval processes, improve key metric reporting, & foster better academic-industry collaboration

Infrastructure for clinical research

- The Netherlands is ranked 11th in the world both in terms of public health and healthcare system quality
- The rise in R&D and healthcare expenditure, particularly between 2019 and 2021, suggests investment in future innovation and quality of services
- A high density of hospitals, particularly in the Randstad region, facilitates the logistics of running trials in the Netherlands

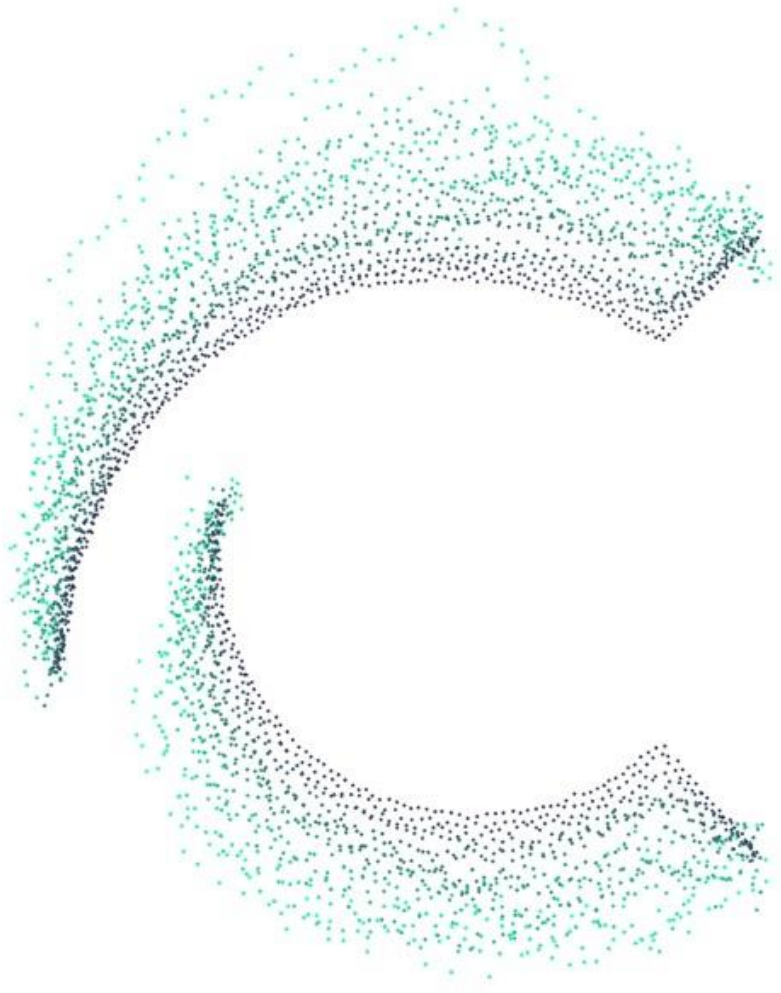
Recommendations

1. Promote the Netherlands' clinical research potential by actively engaging specialists in international conferences and events, enhancing global recognition and fostering knowledge exchange
2. To avoid a bottleneck of resource availability in the future, proactively build a skilled life sciences workforce through collaboration with leading institutions and scholarships and bursaries for related higher education programmes
3. Optimise the efficiency of approvals and start-up times by direct and timely communication with sponsors, start recruitment discussion early, reduce bureaucratic hurdles, and utilise experienced CROs to meet clinical trial deadlines efficiently
4. Create a comprehensive Netherlands-specific clinical trial data dashboard to improve reporting, inform resource allocation, and enhance transparency in clinical research
5. Enhance public perception of industry-sponsored clinical trials in the Netherlands by increasing awareness, engaging the public throughout research, and leveraging patient advocacy groups to foster transparency and positive opinions
6. Promote enhanced collaboration between academic hospitals and industry sponsors by addressing institutional barriers and fostering dialogue through the establishment of a National Life Science Council
7. Create a comprehensive landing page where clinical research networks are categorised.

CITELINE

2. Importance of clinical research

Clinical research explores novel interventions, from drugs to treatment methods, with the aim of assessing their efficacy, safety, and potential to enhance quality of life, ensuring the advancement of medical knowledge and patient care



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Clinical Research and EU Clinical Trial Regulation

Clinical research involves human trials to evaluate the safety and effectiveness of investigational medicines, bridging the gap lab discoveries and patient benefits

Clinical research refers to human studies or trials that are conducted to discover and validate the effects of one or more investigational medicines. It is an important step in the process of bringing new drugs, medical devices, and vaccines to the forefront of medical advancement. It serves as a crucial link between ground-breaking research in the lab and the real advantages that patients can get from these medicines. The safety and effectiveness of potential medicines and vaccines are thoroughly evaluated through a series of rigorously designed clinical trials. These trials, which are divided into several phases, provide important insights into how these new interventions interact with the human body and, ultimately, can shape the future of treatment. In the EU / EEA, approximately 2,800 clinical trials are authorised each year.

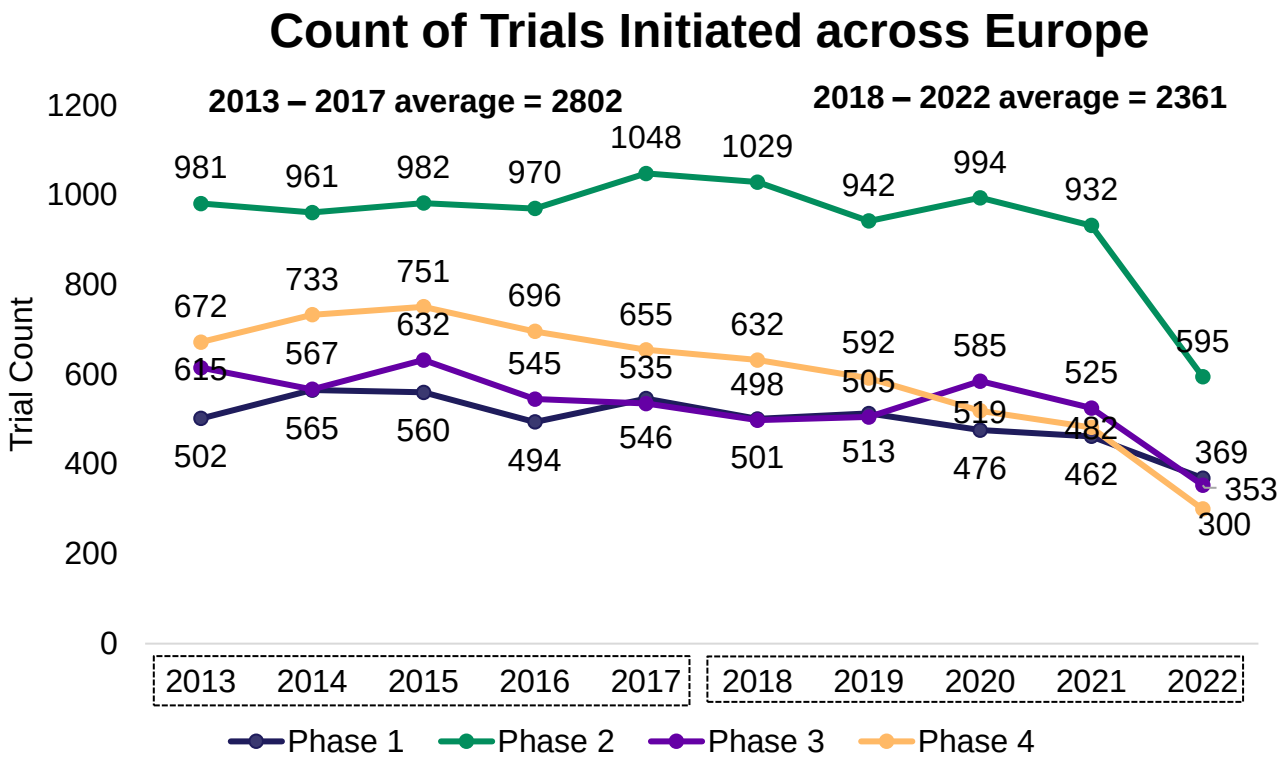
Phase 1 predominantly engages a limited cohort of healthy volunteers, centring on the initial assessment of safety and determination of suitable dosages. As the intervention moves into phase 2, a larger group is studied to assess its efficacy and potential side effects. Phase 3 encompasses an even larger population, aiming to confirm the intervention's effectiveness, monitor its adverse effects, and compare it with existing standard treatments. Once an intervention successfully navigates these phases and obtains regulatory approval, phase 4 comes into play, focusing on post-market surveillance to monitor real-world safety, long-term effects, and broader applications.

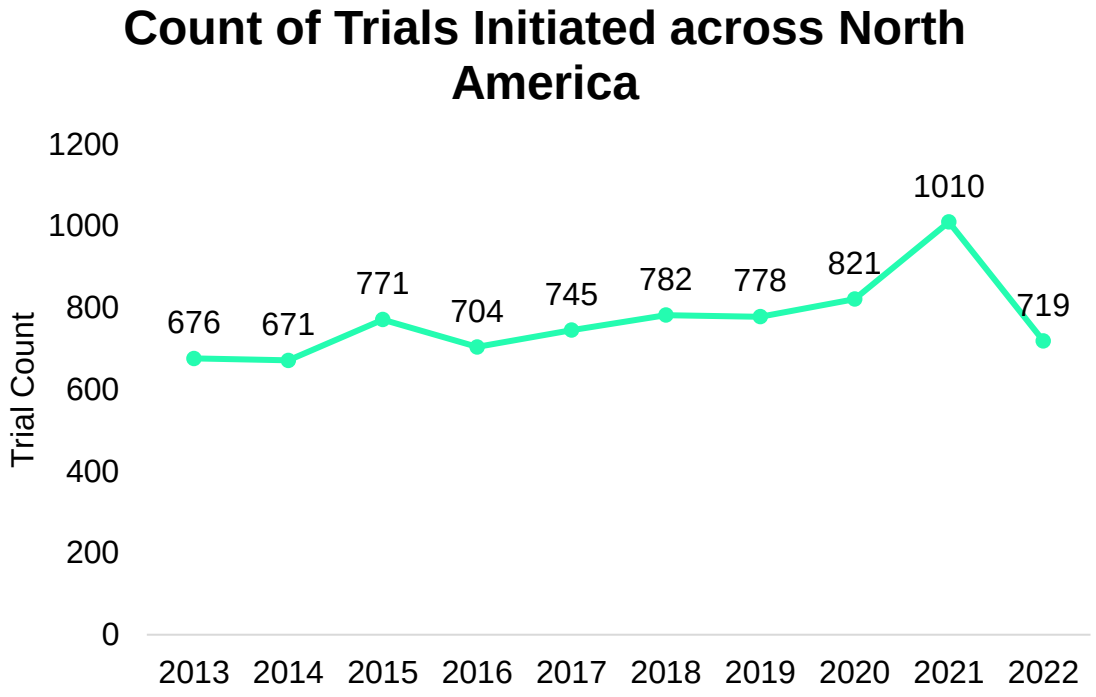
The European Union (EU) pharmaceutical legislation known as the Clinical Trials Regulation took effect on January 31, 2022, repealing the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in EU Member States. The EU Clinical Trial Regulation aims to provide the EU an appealing and suitable environment for large-scale clinical research, with high standards of public transparency and clinical trial participant safety.

Source: EMA; EMA

Comparison of trials conducted in 2013-2017 with 2018-2022

There has been a slight decrease in the number of trials initiated across Europe since the start of the COVID-19 pandemic; average trial initiations dropped by 441 when compared with the previous 5-year period



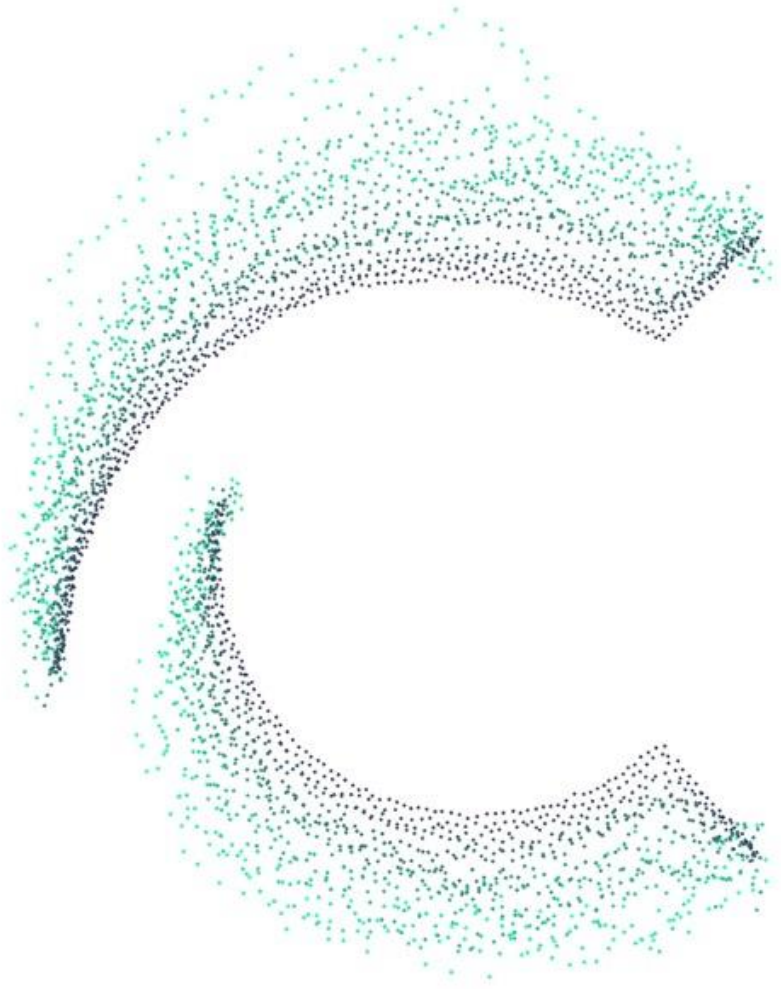


The decline in trials across Europe can be attributed to a variety of factors, including changes in regulatory requirements, such as those relating to data privacy (e.g., GDPR) and clinical trial regulations (e.g., the EU Clinical Trial Regulation), which have made initiating and conducting clinical trials more complex and time-consuming. Additionally, the COVID-19 pandemic disrupted ongoing trials and delayed the initiation of new ones due to safety concerns, travel restrictions, and shifts in healthcare resources, alongside other factors such as heightened costs which have led to fewer trial initiations by sponsors.

Source: Citeline| Trialtrove

CITELINE

3. Key figures on clinical research in the Netherlands



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Key figures on the Dutch Clinical Trials Landscape (1/4)

Top scoring enrolment durations, patient availability and hospital densities are among the vast number of distinct advantages the Netherlands is able to provide as a clinical trial host country

The Netherlands as a clinical trial destination

The Netherlands has long been seen as an attractive country in which to conduct clinical trials. The size of the country facilitates unique advantages for reaching and treating many patients within a small geographic area. The Netherlands boasts a very high doctor-to-patient ratio at 41 doctors per 10,000 of the population (3rd place, narrowly behind Germany & Denmark). This doctor-to-patient ratio is complimented by having the densest population among the comparator countries at 518 people per sq. km of land area. Additionally, any point in the country is, on average, is no further than 5km of a hospital (including outpatient clinics).

The Netherlands has a strong global research presence, ranking 3rd in Europe and 7th worldwide for Highly Cited Researchers in 2022. Additionally, all of its top 10 institutes for clinical, preclinical, and health research are among the European top 100. Interviews with key players in the Dutch clinical research landscape found that this expertise is seen "*across all the therapeutic areas*".

Compared to other countries, The Netherlands is particularly strong for early phase trials (Phase 1 & Phase 2 trials account for ~50% of trials initiated in the country between 2018-2022). For phase 1 and 2 trials, the enrolment duration in the Netherlands is shorter than the European average, and the Netherlands has the 3rd shortest duration among comparator countries. Aside from the previously mentioned population and hospital density advantages, other factors that contribute to fast enrolment of trials in the Netherlands are strong communication and collaboration between Dutch trial stakeholders, and the Centre for Human Drug Research with its "ready-for-research approach," which utilizes a pool of pre-screened patient groups that are on standby for early-stage clinical trials.

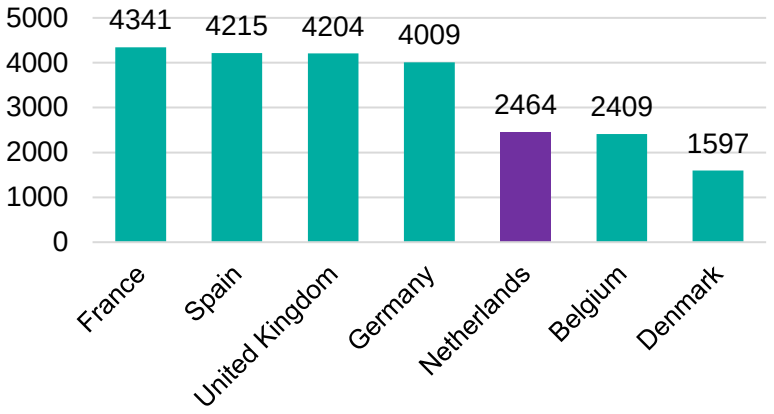
In addition to the early-phase specialism seen in the Netherlands, the country is also an excellent location for indication specific trials; one of just two countries with sub-30 day approval times for ATMP trial. The Netherlands ranks 3rd among comparator countries for ATMP trial count adjusted by population size. The Netherlands leads in patients treated per capita in Oncology trials; it is also competitive in CNS trials, placing 2nd after Denmark. The Netherlands also hosts the most Orphanet rare disease biobanks per 100k of population at 0.18, ahead of Germany at 0.05. Access to rare disease biobanks gives the Netherlands strong positioning within rare disease trials, especially for founder mutation populations in hereditary breast/ovarian cancer and dementia. Within Cardiovascular trials, the Netherlands has shorter enrolment durations than Denmark and France and the country's WCN & VRN cardiovascular KOL networks have been cited as a critically valuable resource for those wishing to conduct cardiovascular research.

Supporting charts for these observations can be seen on the following slides

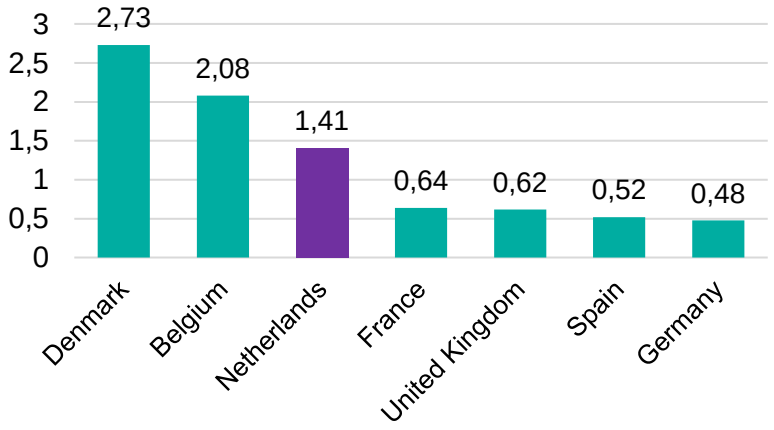
Key figures on the Dutch Clinical Trials Landscape (2/4)

Supporting charts to represent the Dutch Clinical Trial Landscape

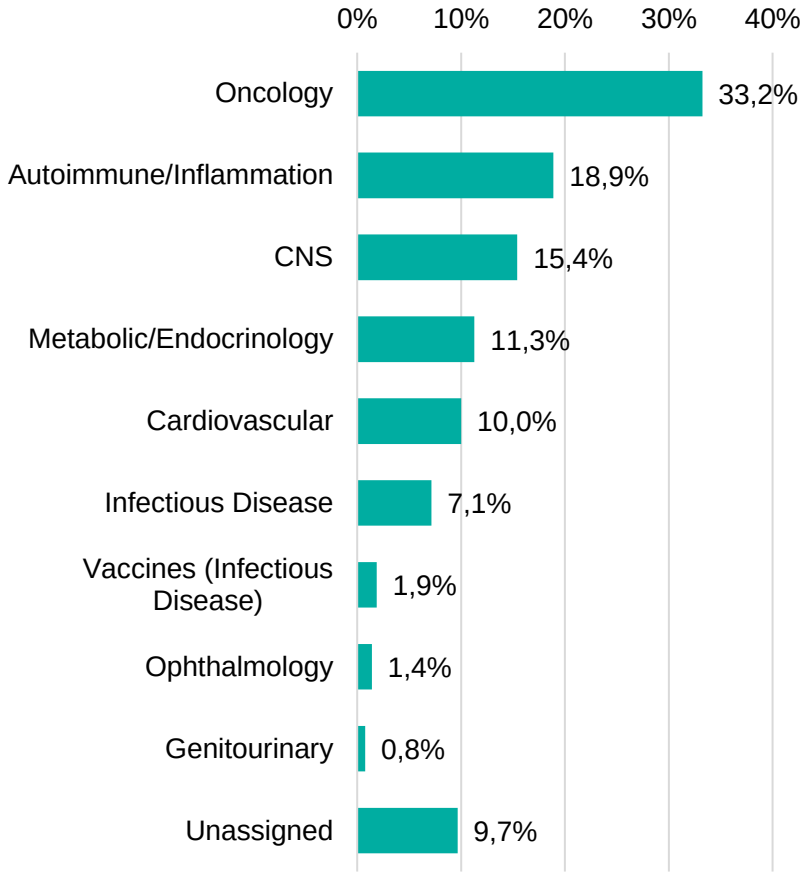
Number of trials initiated (2018-2022)



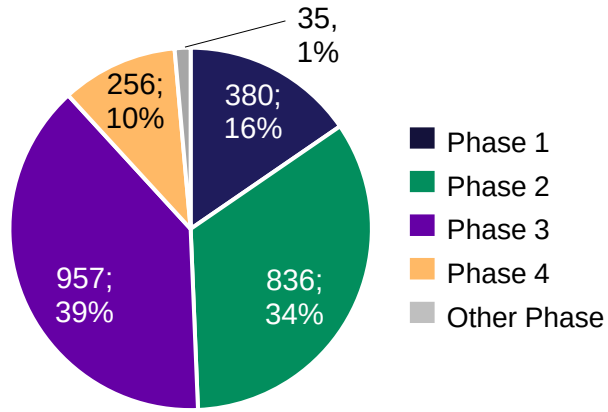
Trial initiations per 10,000 of the population (2018-2022)



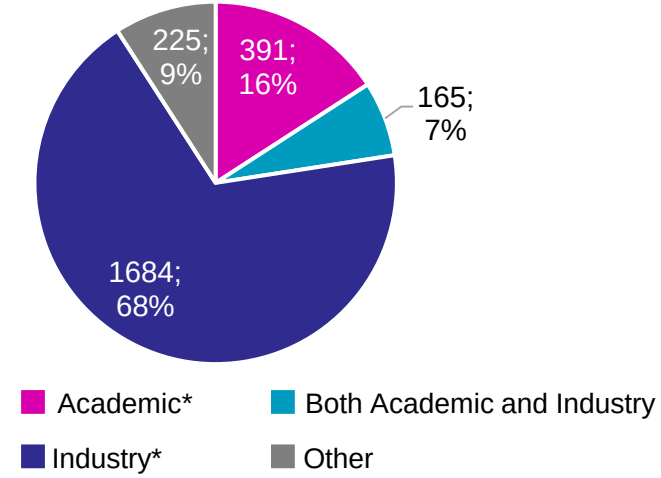
Therapy area proportions, Netherlands (2018-2022)



Dutch trials by phase (2018-2022)



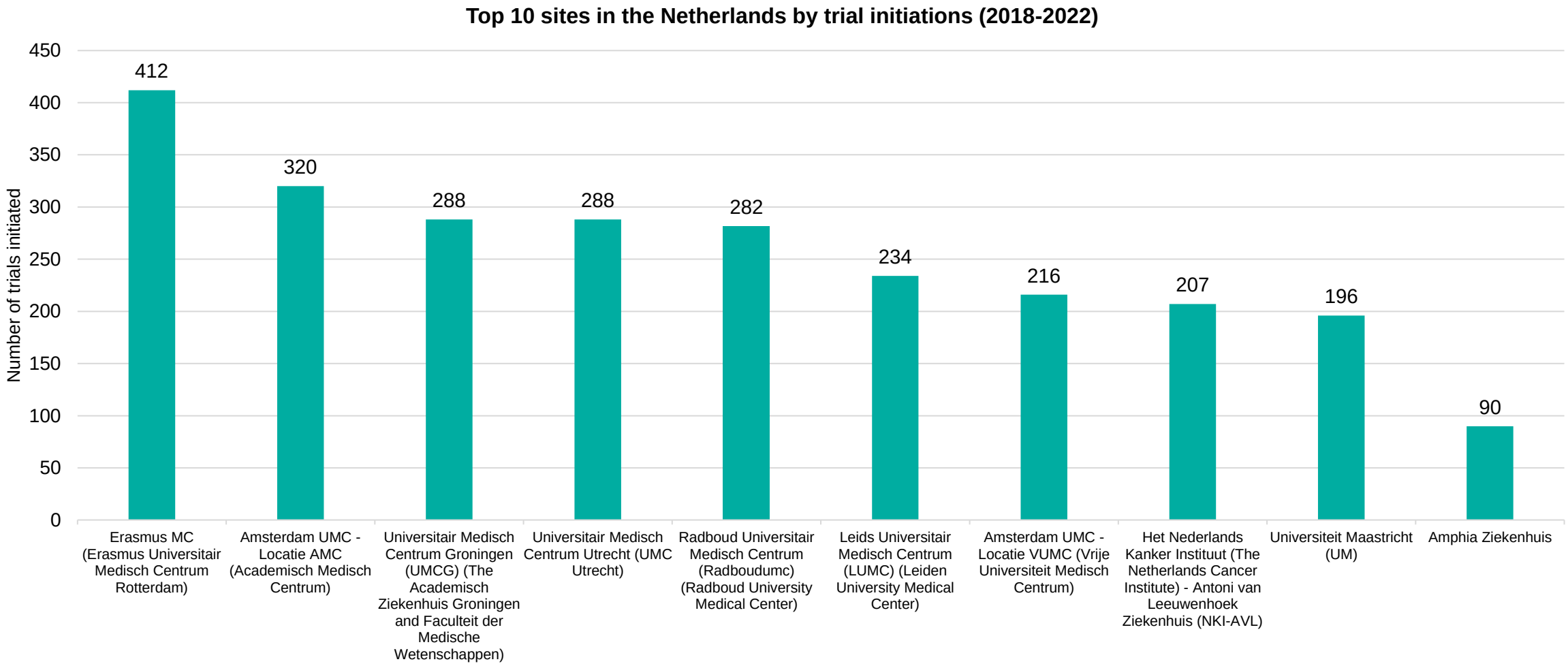
Dutch sponsor type proportions (2018-2022)



*Includes government / cooperative group / miscellaneous / OTC / not for profit collaborations

Key figures on the Dutch Clinical Trials Landscape (3/4)

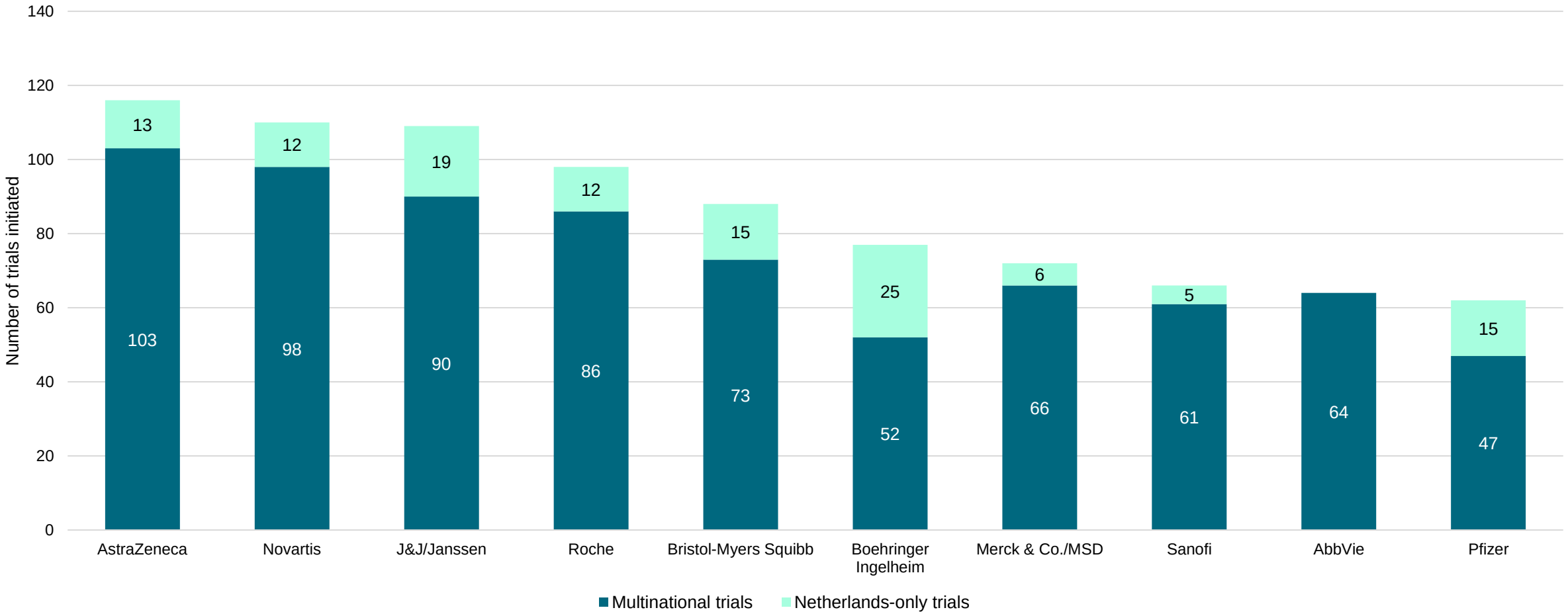
Supporting charts to represent the Dutch Clinical Trial Landscape



Key figures on the Dutch Clinical Trials Landscape (4/4)

Supporting charts to represent the Dutch Clinical Trial Landscape

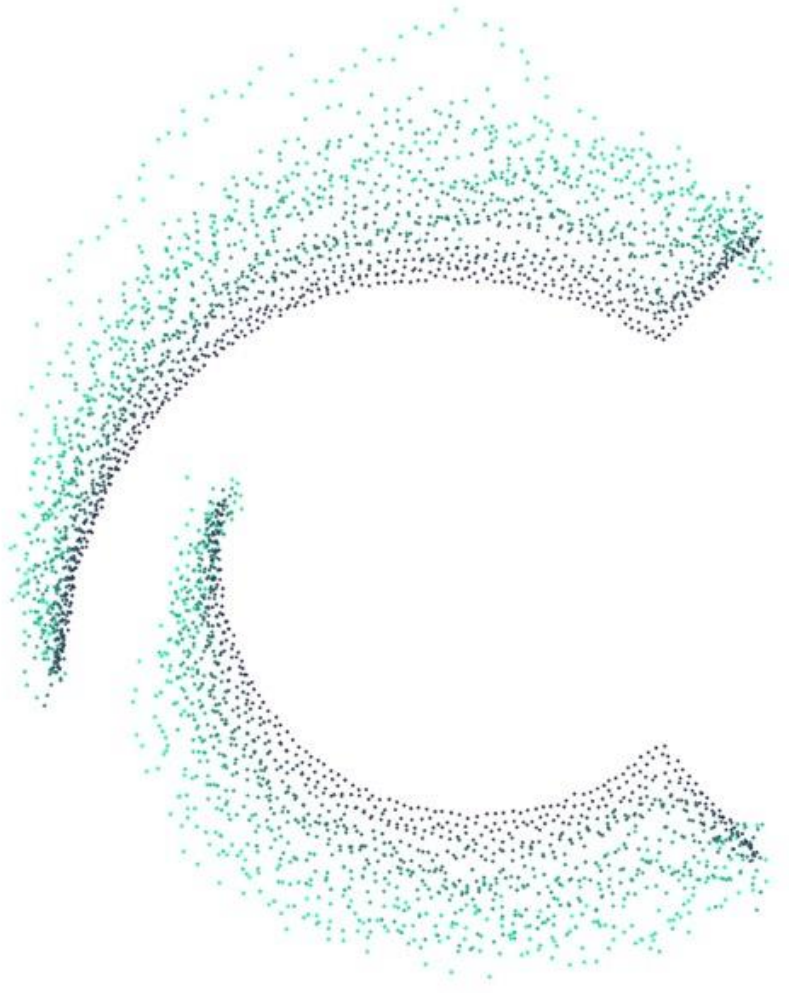
Top 10 industry sponsors in the Netherlands by trial initiation, segmented by multinational vs Netherlands-only trials (2018-2022)



CITELINE

3.1 Ongoing studies, participant counts and financial metrics

Despite a slight decrease in trial initiations across Europe due to the COVID-19 pandemic, the Netherlands stands out, ranking third in both initiated and ongoing trials when adjusted for population in Europe. The country has a strong oncology trials presence, comprising a third of all initiated trials since 2018. While being the fourth most affordable for comprehensive scientific advice, the Netherlands is the second most expensive for basic advice.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Trial initiations by country – population adjusted

The Netherlands has the third highest number of both trials initiated in 2018-2022 and ongoing trials in Europe when adjusted for population

			Population-Adjusted (per 10,000 population)	
Rank	**Number of trials initiated 2018-2022**	**Number of ongoing trials**	**Number of trials initiated 2018-2022**	**Number of ongoing trials**
1	France (4341)	France (3471)	Denmark (2.73)	Denmark (1.91)
2	Spain (4215)	Spain (2996)	Belgium (2.08)	Belgium (1.43)
3	United Kingdom (4204)	United Kingdom (2910)	Netherlands (1.41)	Netherlands (1.04)
4	Germany (4009)	Germany (2669)	Poland (0.67)	Spain (0.63)
5	Italy (3389)	Italy (2502)	France (0.64)	France (0.51)
6	Poland (2514)	Netherlands (1816)	United Kingdom (0.62)	Poland (0.45)
7	Netherlands (2464)	Poland (1688)	Italy (0.57)	United Kingdom (0.43)
8	Belgium (2409)	Belgium (1658)	Spain (0.52)	Italy (0.42)
9	Denmark (1597)	Denmark (1116)	Germany (0.48)	Germany (0.32)

Smaller countries outperform larger countries on number of trials per capita. The Netherlands, for example, has initiated 2.9 times as many trials per capita as Germany, but falls just slightly over half the number conducted by Denmark.

Source: Citeline| Trialtrove

Patient counts in single-country trials across therapy areas and per capita

The Netherlands leads in patients treated per capita in Oncology trials; it is also competitive in CNS trials, placing 2nd after Denmark

	Oncology		Autoimmune/ Inflammation		CNS		Metabolic/ Endocrinology		Cardiovascular		Infectious Disease		Vaccines (Infectious Disease)		Ophthalmology		Genitourinary	
	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K	Sum of Pts	Per 100K
Netherlands	2439	13.9	750	4.3	3179	18.1	890	5.1	1261	7.2	2552	14.6	75	0.4	46	0.3	105	0.6
Germany	4749	5.7	5209	6.3	3514	4.2	5183	6.2	1114	1.3	5283	6.4	21	0.03	0	0	416	0.5
France	5871	8.7	2097	3.1	4067	6	697	1	9482	14	11006	16.2	40	0.1	654	1	617	0.9
UK	2048	3	4742	7	5336	7.9	2202	3.3	3786	5.6	24192	35.9	1182	1.8	108	0.2	580	0.9
Denmark	379	6.5	1257	21.5	3238	55.3	1528	26.1	1292	22.1	1157	19.8	6540*	111.7*	124	2.1	66	1.1
Belgium	455	3.9	2408	20.8	1924	16.6	471	4.1	1665	14.4	2728	23.5	16	0.1	15	0.1	610	5.3

A high number of oncology trials could indicate cancer as major health area of focus in the Netherlands, leading to more extensive research. The emphasis on oncology trials also reflects a substantial investment in oncology research and innovation by industry and academic sponsors. The high number of oncology trials also reflects favourably on the infrastructure and oncology expertise in the Netherlands in comparison to its competitors.

Highest patient count per 100,000 population

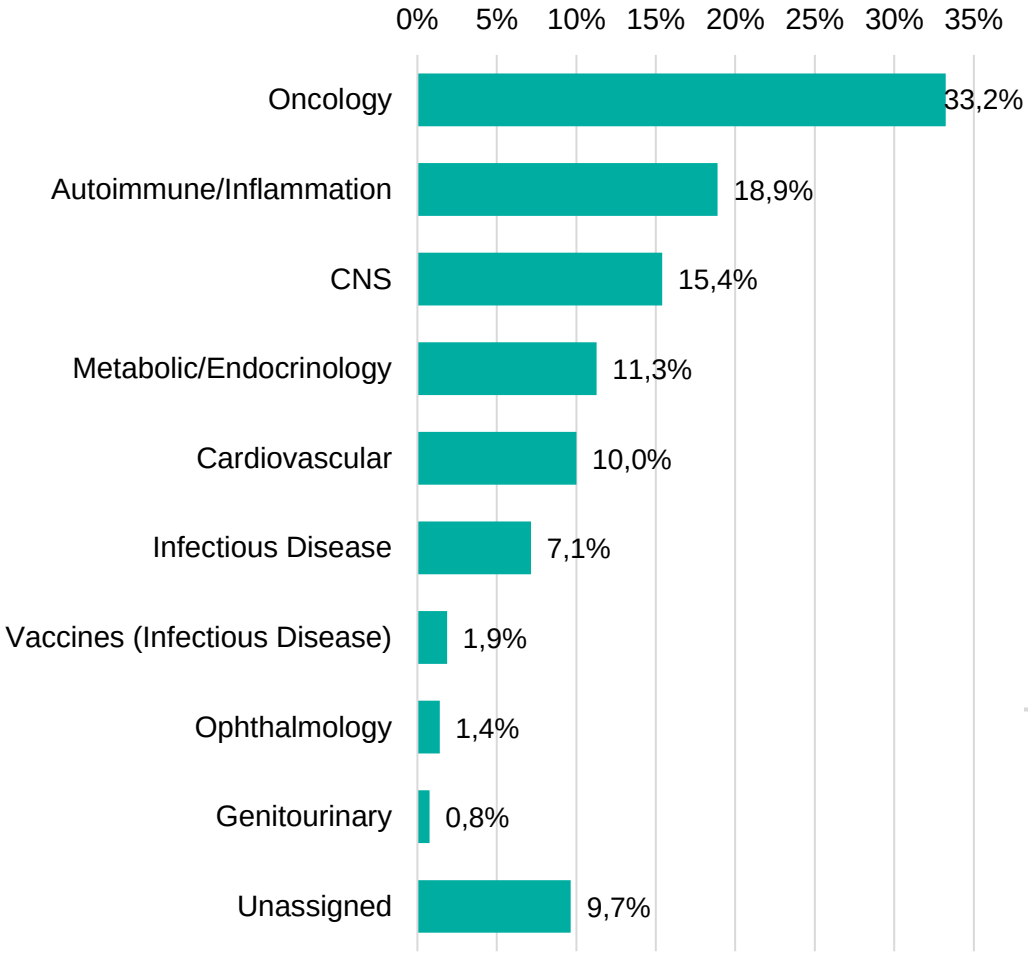
*A single Phase 4 Measles trial is responsible for the high count of patients in Denmark-based Vaccine trials;

Sources: Citeline| Trialtrove

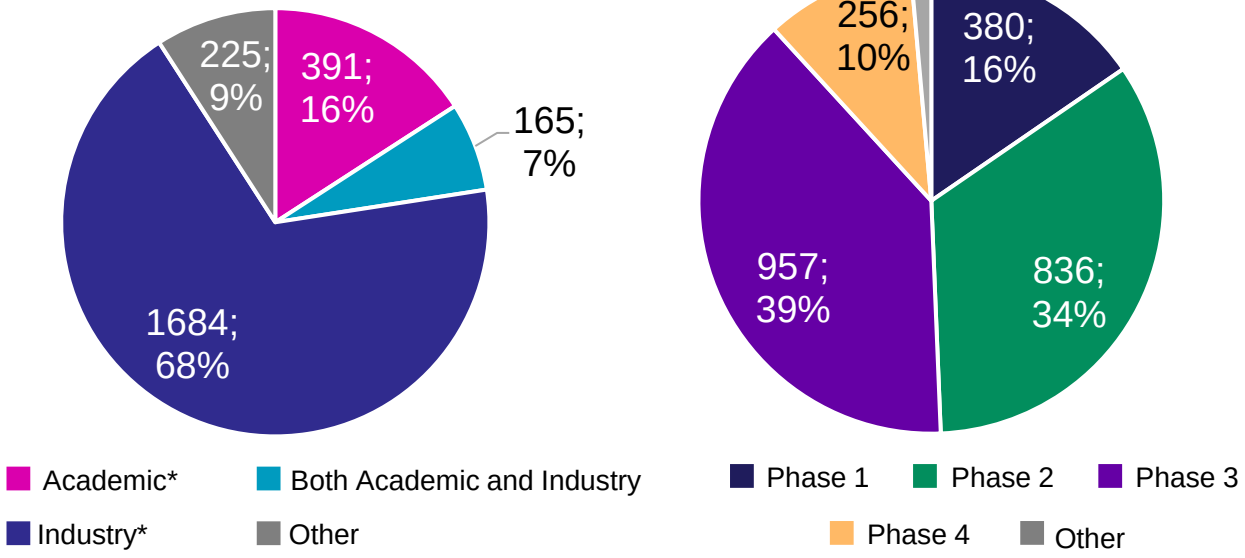
Typology of trials initiated in the Netherlands

Oncology and autoimmune/inflammation trials account for over 50% of all trials in the Netherlands; most trials initiated in the Netherlands have at least one industry sponsor involved, and most trials are in phases 2 or 3

Therapy area proportions, Netherlands (2018-2022)



Sponsor type proportions, Netherlands



Trials by phase, Netherlands

*Includes government / cooperative group / miscellaneous / OTC / not for profit collaborations

In the Netherlands, oncology trials account for one third of all initiated trials. This is followed by autoimmune/inflammation trials and CNS trials. Most of all trials initiated in the Netherlands are phase 3 (39%) followed closely by phase 2 trials (34%). Significantly, over two-thirds of trials initiated in the Netherlands are industry-sponsored.

Source: Citeline| Trialtrove

Fees for scientific advice

Among the five comparator countries and the EMA, the Netherlands is the fourth least expensive for comprehensive advice and the second most expensive for basic advice

Country	National Competent Authority	Lowest Fee	Lowest Fee Service	Highest Fee	Highest Fee Service
-	*EMA*	26,200 EUR	Follow-up to an initial request on quality development, safety development, or bioequivalence studies for generic medicinal products	103,800 EUR	Initial requests for scientific advice on quality + safety + clinical development, or quality + clinical development, or safety + clinical development, or qualification advice
Belgium	*FAMHP*	2,582 EUR	Maximum one question. Written scientific/technical/regulatory advice concerning e.g. chemical, pharmaceutical or (pre)-clinical aspects, the statute of a medicinal product, investigational medicinal product (IMP) vs. non-investigational medicinal product (NIMP) statute, naming (umbrella brands), GMP aspects	20,656 EUR	1) Mixed advice concerning both technical/regulatory questions and scientific questions; 2) Scientific advice on multiple expertise domains e.g., expertise domain 1 (chemical/pharmaceutical aspects), expertise domain 2 (clinical, non-clinical aspects), or expertise domain 3 (protocol assistance); 3) Advice on early market access aspects of a medicinal product; 4) Joint Scientific Technical Advice (e.g., with other Belgian Health Authorities or other HTA bodies in the EU)
Netherlands	*Medicines Evaluation Board*	6,860 EUR	Simple advice (regulatory advice, advice regarding the pharmaceutical or preclinical aspects of the medicinal product, or follow-up advice)	15,650 EUR	Complete multidisciplinary advice (advice regarding the clinical, preclinical, and pharmaceutical aspects of the medicinal product)
Denmark	*Danish Medicines Agency*	17,800 DKK (2,390 EUR)	Simple advice (regulatory, CMC, or preclinical)	35,000 DKK (4,699 EUR)	Multidisciplinary covering all areas (regulatory, CMC, preclinical, and clinical)
Germany	*BfArM*	Free	The BfArM does not charge any fees for pre-submission Meetings regarding centralised European Procedures	18,000 EUR	Details not specified, however advice to drug applicants can range from 1000 to 18,000 EUR
UK	*MHRA*	Free	Discussion on development for paediatric forms and uses meeting criteria for waiver set down in schedule 5 paragraph 10 of SI 2008 No. 552	4,936 GBP (5,522 EUR)	Quality, safety, and clinical development advice
France	*ANSM*	Free	N/A	Free	N/A

Lowest and highest fees do not take into account incentive-type reductions e.g., for small companies

Sources: EMA; FAMHP; Medicines Evaluation Board; Danish Medicines Agency; BfArM; MHRA; ANSM

Clinical trial application costs

Similarly to scientific advice, France offers a free process to register clinical trials with its national competent authority; Belgium is the only other country out of the 6 comparators to share this clinical trial benefit

	Cost of Clinical Trial Application	Additional Notes on Clinical Trial Costs
Netherlands	• *Part 1-As concerned member state:* **€1,520** (non-commercial), **€4,560** (commercial) • *Part 1-As reporting member state:* **€2,280** (non-commercial), **€6,840** (commercial) • *Part 2-Member state-specific documents / IMDP (for unregistered product) for national and reporting member state research :* **€760** (non-commercial), **€2,280** (commercial) • *Annual safety report / Development safety update report:* from **€190** to **€2,850**	• For each type of clinical trial review, reduced commercial and non-commercial rates are provided for resubmissions of complete dossiers (i.e. post-withdrawal, lapsed submission or a negative decision) • Fees apply for substantial modifications from **€570** to **€2,280**
Germany	• First phase 1-3 submission: **€3,800** basic fee • Follow-up study phase 1-3: **€1,500** to **€2,100** • Approval of a trial for a drug that already has MA in EU member state: **€1,700** basic fee • Approval of trials for drugs containing genetically modified organisms(s): **€9,500**	• Additional fees of **€800-900** added on top of basic fees for submission of an integrated study protocol with additional sub-studies • Approvals of variations to trials after study start: **€730** to **€1,100** • Assessment of annual reports: **€500** to **€2,500**
UK	Ranges **from €282** (applications without an IMPD) **to €3,833** (applications with an IMPD)	€282 also applies for CT variations/amendments and assessment of annual safety reports. No annual clinical trial fees
Denmark	• *Single-country trials*: **from €8,808** for drugs which have MA in an EU or ICH country, **to €13,386** for applications with an IMPD • *As additional member state:* **from €8,091** for drugs which have MA in an EU or ICH country **to €9,301** for applications with an IMPD • *As reporting member state:* **from €10,422** for drugs which have MA in an EU or ICH country **to €16,935** for applications with an IMPD • *Trials approved under directive cf executive order no 101 of 18th Jan 2022:* **from €3,430** for drugs which have MA in an EU or ICH country **to €6,809** for applications with an IMPD	• There is a reduced fee of **€5,261** for phase 1 trial applications • If the IMPD is highly simplified, or the investigational drug is a modification of a drug for which a MA has been issued and the modification only concerns packaging, labelling, shape or appearance, fees are the same for new drugs as marketed ones • Fees apply for substantial modifications from **€1,328** to **€2,765** • Annual fees are applicable at a fee of **€1,786** (phase 1 exempt)
France + Belgium	**Free**	

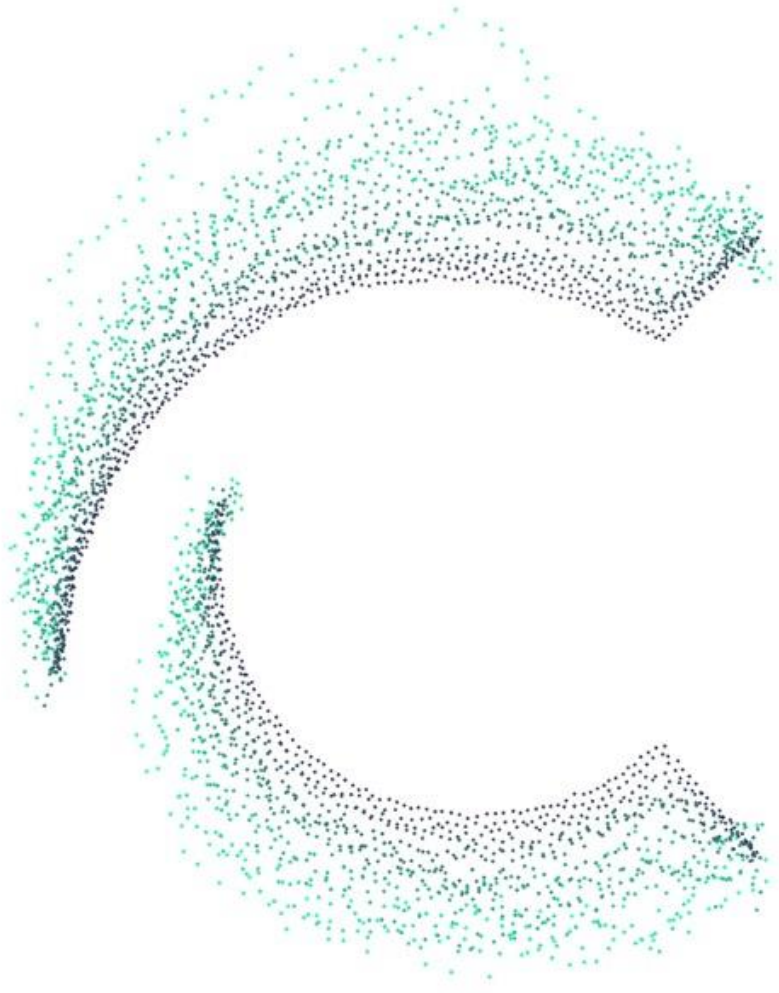
Sources: HBW Insight, France cuts clinical trial fees; pharma.be; Current MHRA Fees, MHRA; Fees for clinical trials, Danish Medicines Agency; CCMO; AMG Cost Ordinance, BfArM; Citeline Primary Research. Key players were interviewed for their insights, n=6

Abbreviation: IMPD = Investigational Medicinal Product Dossier; MA = Marketing Authorisation; ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

CITELINE

3.2 Key figures for academic excellence

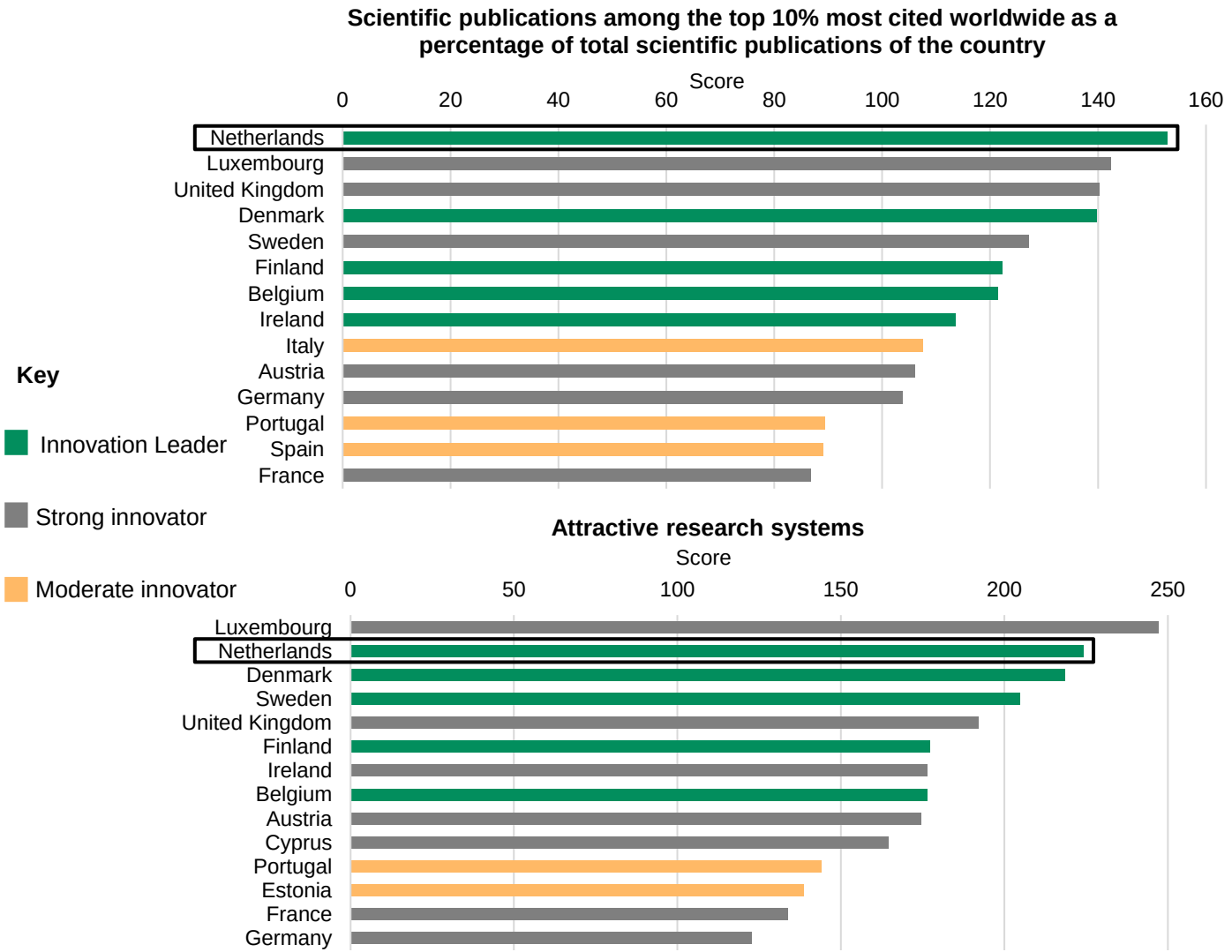
The Netherlands excels in research and is recognised as as an innovation leader in Europe. The Netherlands has a strong global presence, ranking 3rd in Europe and 7th worldwide for Highly Cited Researchers in 2022. Additionally, all of its top 10 institutes for clinical, preclinical, and health research are in the European top 100.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Academic Innovation

The Netherlands has the greatest proportion of its publications occupying the top 10% most cited worldwide and ranks second in Europe as an ‘Innovation Leader’ for the attractiveness of its research systems



The European Innovation Scoreboard (EIS) assesses the strengths and weaknesses of European and surrounding countries' innovation systems. It is an invaluable tool for countries seeking to enhance their performance. According to EIS, the Netherlands is an Innovation Leader, outperforming the EU average by 129%.

The Netherlands is the best Innovation Leader for scientific papers in the top 10% most cited worldwide, which is a measure of the research system’s impact because highly cited publications are regarded to be of higher quality. The Netherlands also ranks high in terms of the attractiveness of its research systems, which measures the international competitiveness of the science base by examining international scientific co-publications (2021), most cited publications (2019), and foreign doctorate students (2020).

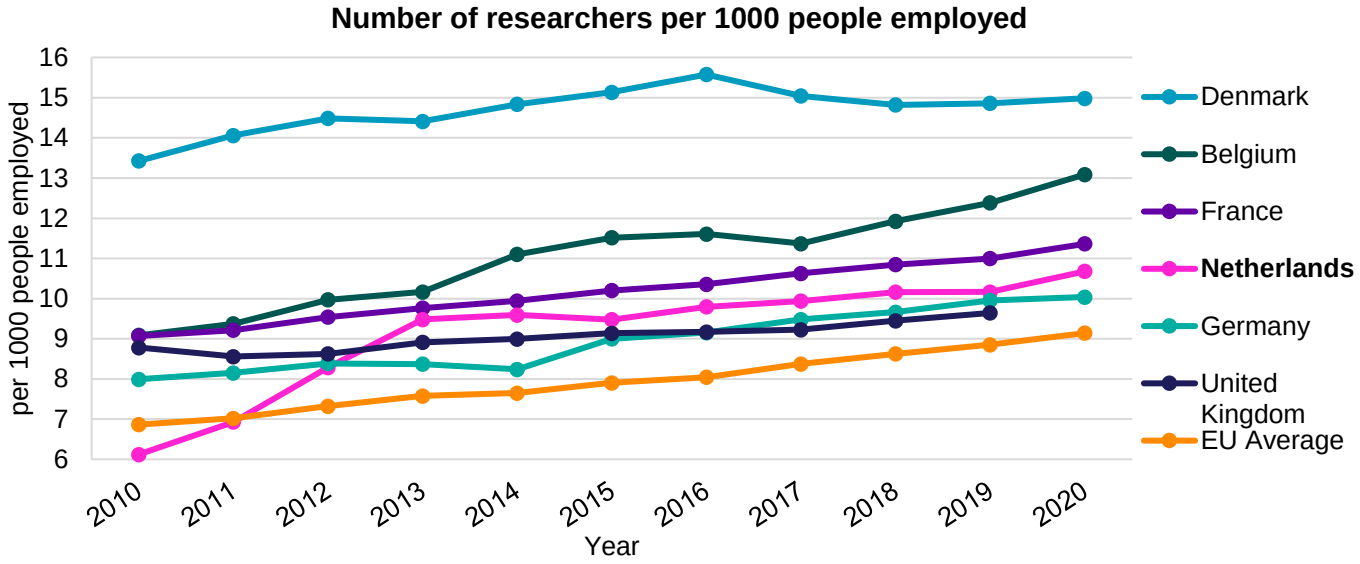
The Netherlands’ high ranking solidifies its reputation as a hub of academic excellence and global scientific competitiveness.

Source: European Commission European Innovation Scoreboard 2022; EIS Country Profile; N.B Only EU and United Kingdom included in analysis

Highly cited researchers and researchers per 1000 people employed

Despite a mid-range position among other EU countries in researchers per 1000 employed, the Netherlands ranks 3rd in Europe and 7th globally for Highly Cited Researchers in 2022, occupying 2.9% of the world share

Rank	Country/Region	Number of Highly Cited Researchers (2022)	World Share (%)
1	United States	2764	38.3
2	China, Mainland	1169	16.2
3	United Kingdom	579	8.0
4	Germany	369	5.1
5	Australia	337	4.7
6	Canada	226	3.1
7	**Netherlands**	**210**	**2.9**
8	France	134	1.9
9	Switzerland	112	1.6
10	Singapore	106	1.5



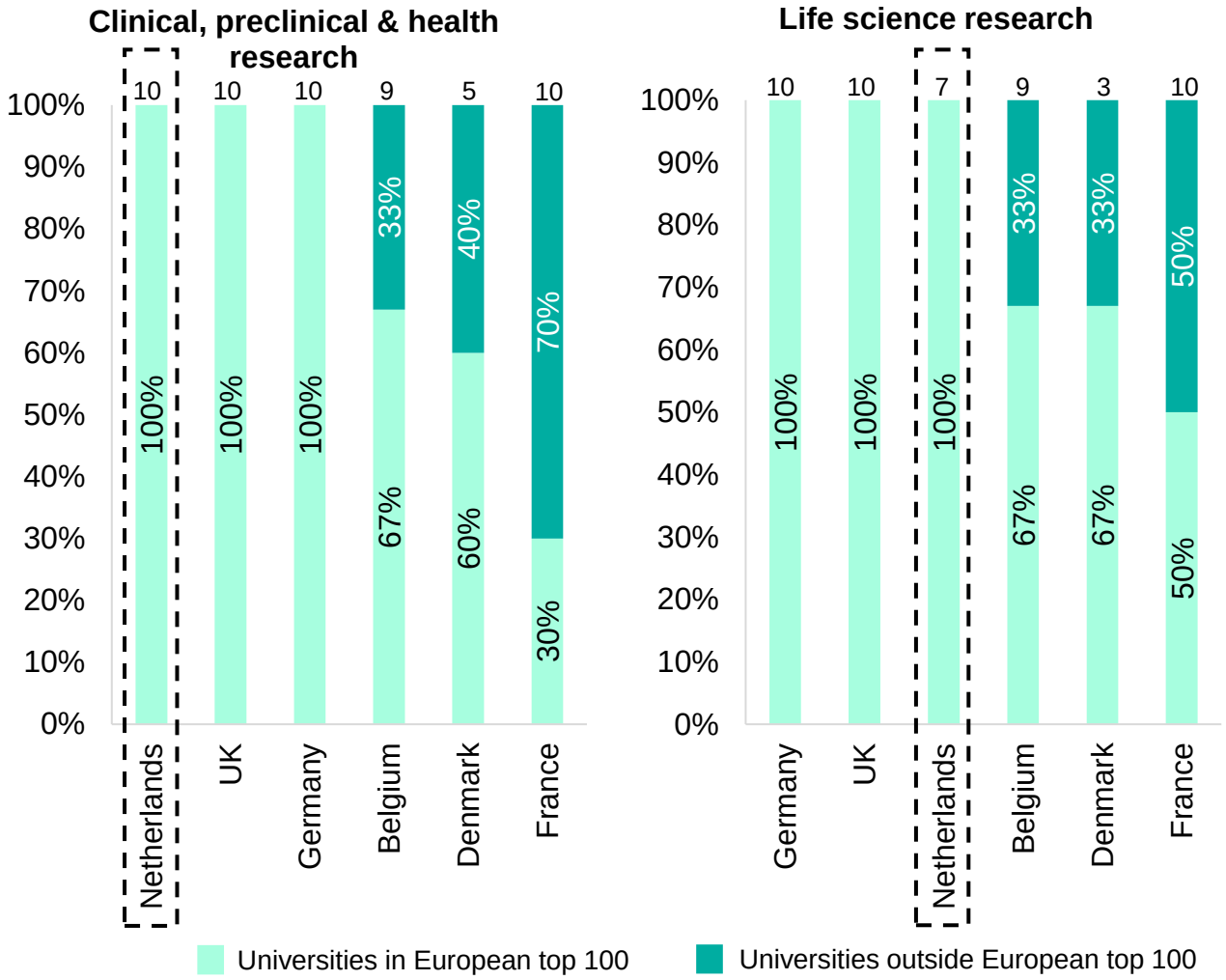
Source: OECD; Clarivate; Citeline Primary Research. Key players were interviewed for their insights, n=6

Researchers are professionals in science and technology who contribute to generating new knowledge, products, processes, methods, and systems, while also overseeing the related projects. The Netherlands' ranking in the top 10 counties globally in the Clarivate™ Highly Cited Researchers indicates a strong presence of influential and impactful scientific contributions. Highly Cited Researchers have proven their influence with numerous top 1% cited papers in science and social science journals between 2011 and 2021.

In an interview that Citeline conducted with key players in the clinical research field within the Netherlands, one key player stated that "*the density of global scientific leaders in the Netherlands is high compared to the other countries, and you see this across all the therapeutic areas*". This claim is validated by data and is a clear advantage for the Netherlands in clinical research. Despite its relatively smaller size, the Netherlands has a rich pool of skilled researchers, contributing to its high science and social science research performance compared with larger European countries such as Germany and the United Kingdom and the EU on average.

Times Higher Education World University Rankings – Top research institutes

100% of the Netherlands' top 10 institutes for clinical, preclinical & health research have scored in the EU top 100; this same proportion is seen for the country's 7 assessed life science research institutes



Universities in European top 100 | Universities outside European top 100

Top 10 Dutch Universities
Erasmus University Rotterdam*
University of Amsterdam
Maastricht University*
Utrecht University
Leiden University*
Vrije Universiteit Amsterdam
University of Groningen
Radboud University Nijmegen
Wageningen University & Research
Delft University of Technology

*Institutes not among the Netherlands' top 7 life science research institutes

In the clinical, preclinical, and health research segment of the Times Higher Education World University Rankings 2023, the European category comprises 559 universities. All leading Dutch universities are in the EU's top 100. Similarly, in life sciences, all 7 Dutch universities in the ranking are in the European top 100. Criteria include research influence, volume, reputation, and the learning environment.

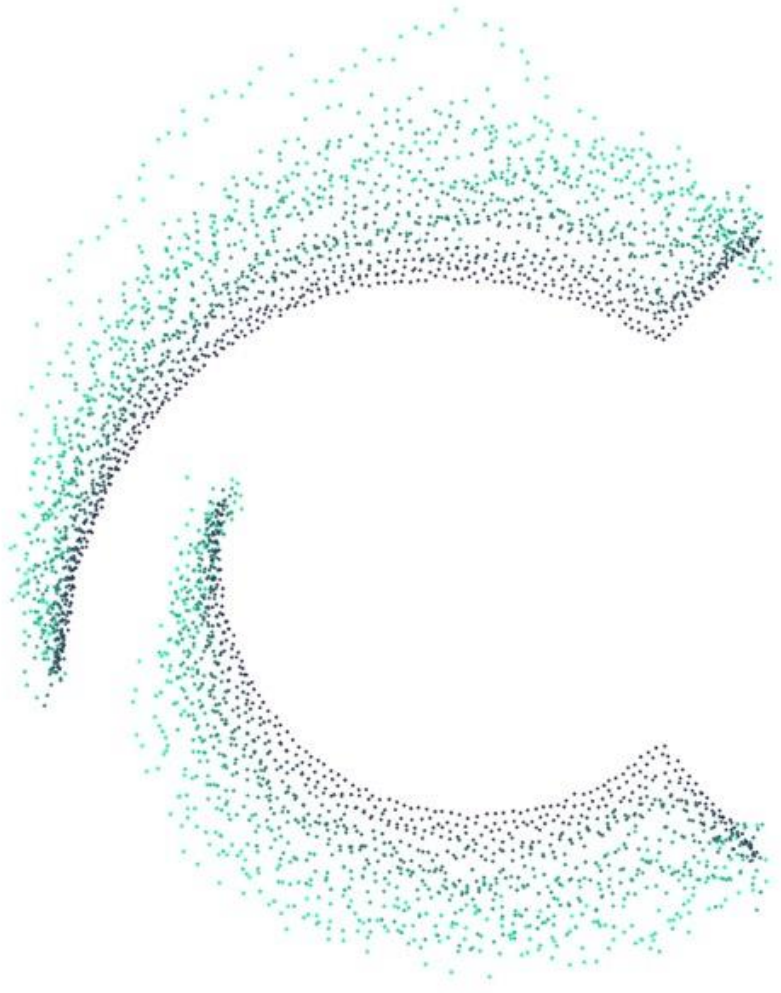
Aside from Delft University of Technology and Wageningen University & Research, each listed university is affiliated with an academic hospital. These affiliations highlight these institutions as centres of excellence, integrating high-quality patient care, teaching, research, and education.

Source: Times Higher Education - Clinical and Health Research; Times Higher Education - Best European Universities

CITELINE

3.3 Key figures for ease of conducting trials

The Netherlands has competitive clinical trial start-up timelines, notably so for ATMPs where the Netherlands is one of only 2 countries among EU comparators to approve an ATMP trial in less than 30 days. Recruitment time in phase 1 and 2 clinical trials is particularly competitive, with factors such as strong stakeholder communication and high population density contributing to the fast enrolment speeds.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Trial approval times

The Netherlands is competitive in clinical trial start-up timings, with ATMP approval timelines being a specific opportunity for differentiation among other EU countries

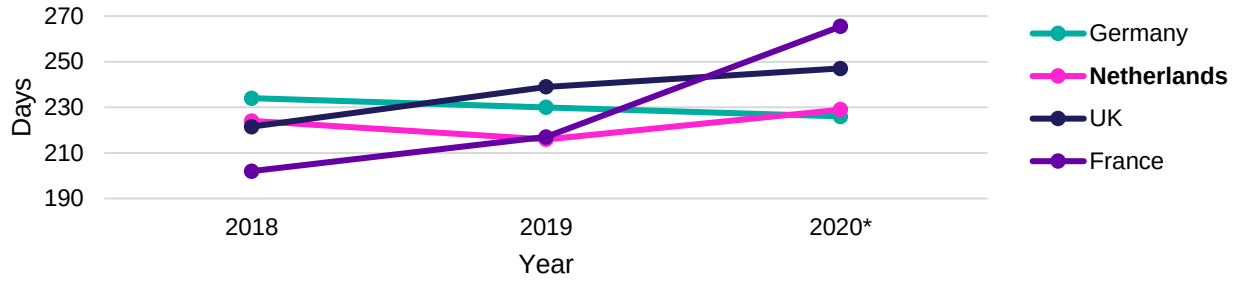
Time from trial application to first patient dosed

When measured by the median time from clinical trial application to a regulatory authority and the first patient receiving a first dose for a subset of commercial trials from 25 pharmaceutical companies across all phases, the Netherlands was the fastest among comparators in 2019, and second fastest in 2020. The fast clinical trial start-up timings could be in part due to competitive clinical trial agreement execution timings, as three out of four key players interviewed by Citeline said they are satisfied with clinical trial execution timing in the Netherlands. Study start-up time is an important metric for sponsors and CROs and could be a costly bottleneck if drawn out.

ATMP trial timings

From analysis of 26 ATMP trials initiated between 2014-2019, 18 of which were multinational, the Netherlands was noted to be one of only two countries in which ATMP trials have been approved in less than 30 days, highlighting ATMPs as a particular therapy area in which the Netherlands can stand out in terms of timelines.

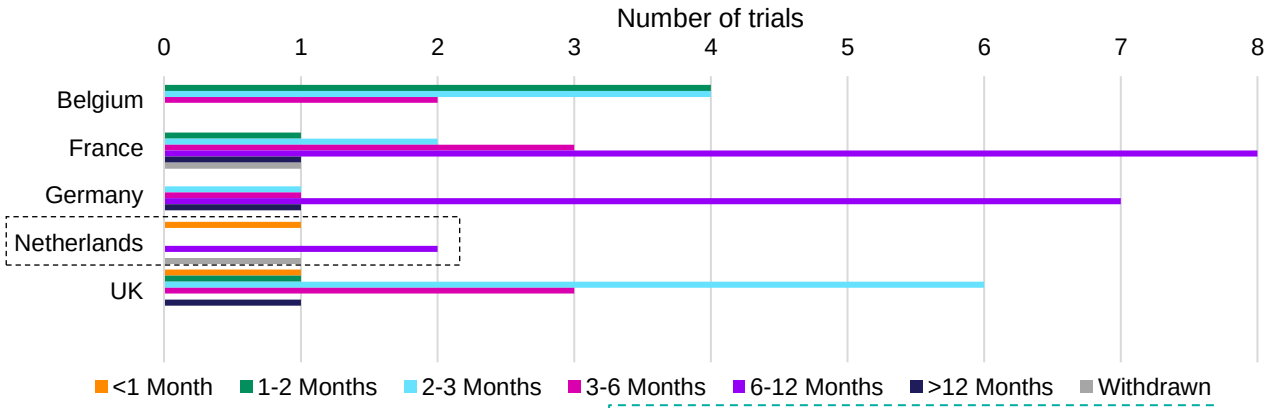
Median time from trial application to first patient dosed



Number of trials included in the analysis of median time from trial application to first dose

Country	2018	2019	2020
Germany	93	125	95
Netherlands	**41**	**55**	**43**
UK	92	98	79
France	75	105	86

ATMP Clinical Trial Approval Times



* 2020 timings likely affected by COVID-19 pandemic

Sources: UK Government Life Science Competitiveness Indicators 2022; Alliance of Regenerative Medicine

ATMP trials

The Netherlands is ranked 3rd among comparator countries for ATMP trial numbers adjusted by population size, and has invested in resources and cross-border collaborations to foster ATMP development and access

Rank	ATMP trial numbers adjusted for population size (per 10,000)
1	Belgium (0.07 trials)
2	Denmark (0.05 trials)
3	Netherlands (0.05 trials)
5	UK (0.02 trials)
6	France (0.02 trials)
7	Germany (0.02 trials)

"Our medical expertise is very much advanced when you're talking about ATMP trials. I certainly think that Netherlands is an attractive country."

The Netherlands is very engaged with the advancement of ATMP opportunities, with the RegMed XB cross-border collaboration of ~500 Dutch and Belgian scientists, multiple centers of excellence including the NecstGen research and development center established in 2020, and involvement in BeNeLuxA to improve ATMP access post-approval.

These efforts are reflected in the Netherlands' 3rd place ranking among comparator EU countries by number of ATMP trials adjusted for population size. This is further supported by the fact that all the key players Citeline interviewed felt the Netherlands is an attractive environment for ATMP trials due to logistical co-ordination, advanced research and medical expertise, and authorities being open to discussions and innovation.

This expertise, combined with the Netherlands' speed in ATMP trial approvals, provides a particular opportunity for the Netherlands to be positioned as a forerunner in ATMP trial conduct.

Sources: Citeline| Trialtrove; Erasmus MC; University of Galway; Lund university; BeNeLuxA; Citeline - Pink; Citeline – Scrip; Leiden university; Citeline - Pink 2 ; Citeline Primary Research. Key players were interviewed for their insights, n=6

Enrolment rate and duration – single country trials

The Netherlands stands out among comparator EU countries in terms of early-stage trial recruitment duration and late phase enrolment rate

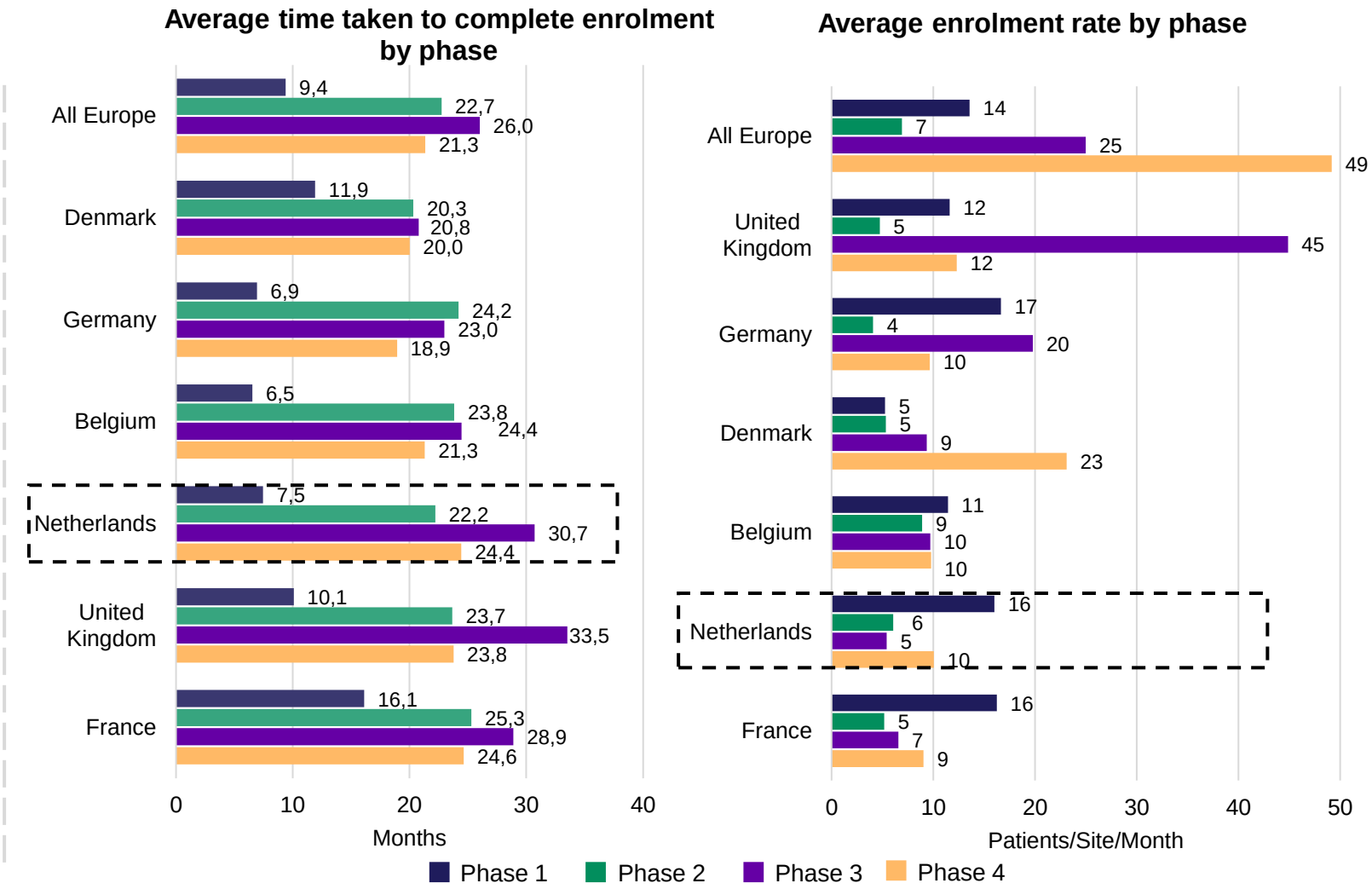
Enrolment duration

For phase 1 and 2 trials, the enrolment duration in the Netherlands is shorter than the European average, and the Netherlands has the 3rd shortest duration among comparator countries

Enrolment rate

When judged by enrolment rate, the Netherlands is also ranked 3rd among EU comparator countries for phase 4 trials.

Factors that help speed up enrolment in the Netherlands include having a high population and hospital density, strong communication and collaboration between Dutch trial stakeholders, and the Centre for Human Drug Research and its "ready-for-research approach," which uses a pool of key pre-screened patient groups that are on standby for early-stage clinical trials.



Note: U.K. phase 3 enrolment are particularly high due to COVID-19 trials with high patient volume & low site numbers

Sources: Citeline| Trialtrove; Centre for Human Drug Research; GCP Mindset, Clinical Trials in the Netherlands and Belgium

Ease of working with clinical trial stakeholders

Openness to collaboration and ease of access, facilitated by a strong landscape of research networks, stand-out as advantages of working with Dutch clinical trial stakeholders in the opinion of interviewed key players

Regulatory agencies	CROs and Manufacturers	Patient advocacy groups
▪ Easy to access, including the ethics committee ▪ Easy to ask and receive feedback	▪ Many new CRO players	▪ Easy to access and have mutual goal with industry, so can be open for collaboration across multiple stakeholders

Scientific leaders	Hospitals	Inter-country collaboration
▪ Mutually aligned to keep innovation at a high level	▪ Easy for hospitals to connect with manufacturers and pharmacies due to geographic size	▪ Important for multicentre studies ▪ Strong on an EU level (centralised EU regulatory system)

Across the key players that were interviewed by Citeline, it was found that overall Dutch clinical trial stakeholders are easy to access and open to collaboration. Stakeholders are mutually aligned to strive for excellence, are open-minded when it comes to innovation, and are generally quick to respond.

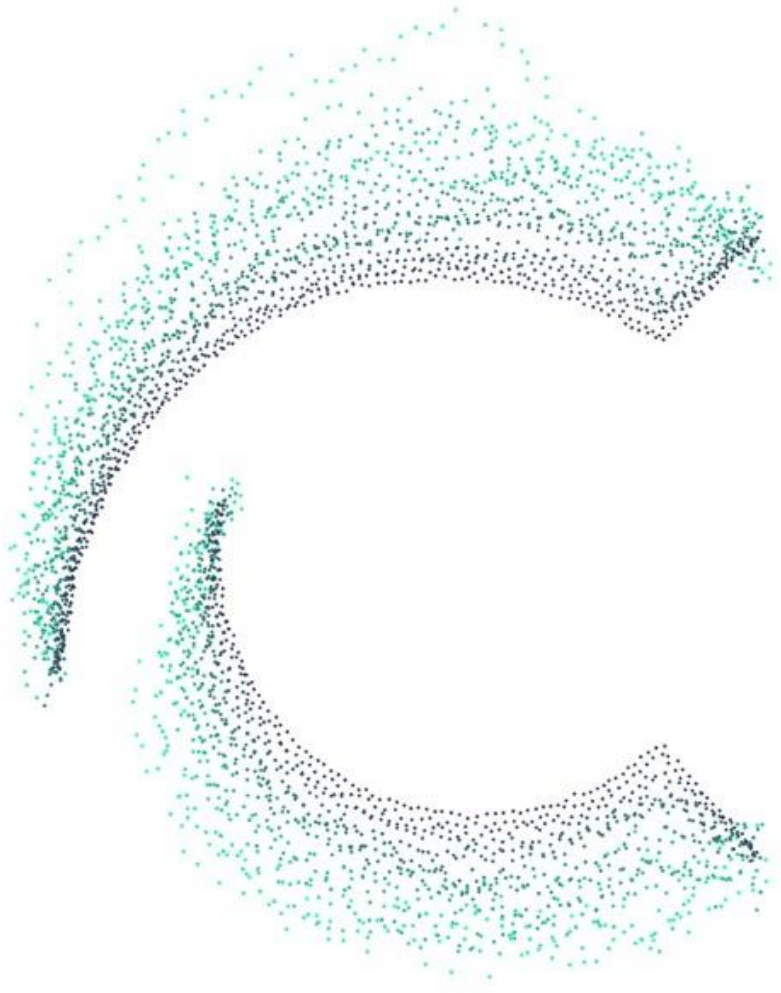
The Netherlands also benefits from a rich clinical research network which facilitates collaboration. In particular, there are numerous oncology networks split by region, which aim to increase collaborative efforts and knowledge share. Examples include Oncomid, OncoZon (Southeast Netherlands), OncoNoVo+ (North Holland/Flevoland region). One key player said of the oncology networks: *"within oncology you also see that there are certain diseases where we really excel compared to the others. In prostate cancer, bladder cancer and phase 1 oncology those research networks are really well organised."*

Sources: Citeline Primary Research. Key players were interviewed for their insights, n=6

CITELINE

3.4 Key figures for availability of patients

The Netherlands' high population density is complemented by physical infrastructure including the largest paediatric oncology facility and the most numerous rare disease biobanks per capita in Europe. Additionally, the country has the most oncology patients per 100K of the population and ranks 1st for enrolment duration of phase 1 & phase 4 industry-sponsored trials, and 1st for enrolment rate of phase 1 academic-sponsored trials



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Population density and patient data availability

The small country size and large population density of the Netherlands facilitate easy travel to trial sites

Size & density

- The Netherlands is the most densely populated among the surrounding countries, at 518 people per square km of land, considerably greater than the comparably sized countries of Belgium & Denmark
  - This density greatly improves access to patients who are often clustered in centralised locations around trial sites
- The geographically small size of the Netherlands offers unique advantages to patients in terms of the distance they commute for treatment
  - Avoiding prolonged travel enhances the quality of life for trial participants

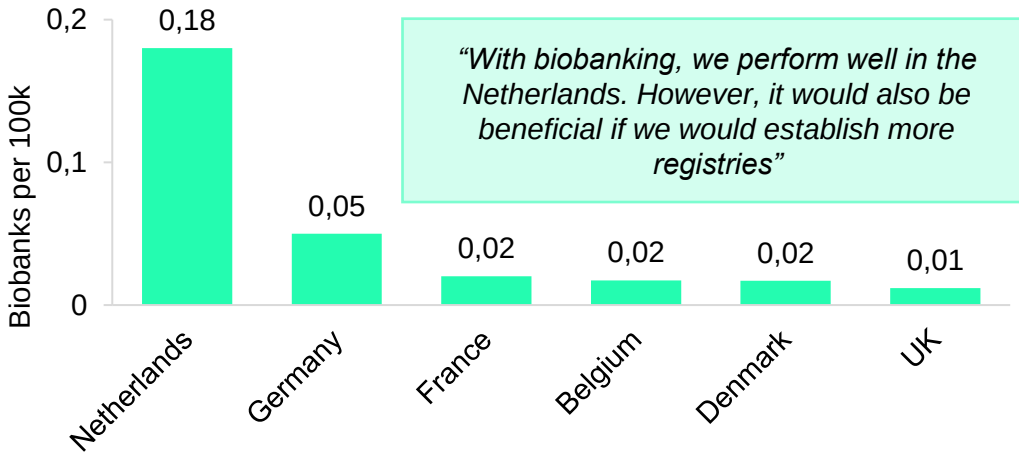
Biobanks & registries

- The Netherlands has the most Orphanet rare disease biobanks per 100k of population at 0.18 (absolute count 32), ahead of Germany at 0.05 per 100k (absolute count 39)
  - Access to rare disease biobanks provides the Netherlands strong positioning within rare disease trials, especially for founder mutation populations in hereditary breast/ovarian cancer and dementia
- The Netherlands has over 40 national patient registries, on par with the UK (43 national registries) and ahead of Belgium (38) and Denmark (2)
  - Key players interviewed by Citeline feel that increasing registry counts in the Netherlands would yield further benefits for conducing trials

Country	People per sq. km of land area (2020)	Total population (2021)
Netherlands	**518**	**17.5M**
Belgium	381	11.6M
United Kingdom	277	67.3M
Germany	238	83.2M
Denmark	146	5.9M
France	123	67.7M
European Average	112	-

"It is relatively easy to get a patient to participate in a study if the site is a short commute, whereas when you talk about a larger, less densely populated country, then that travel becomes a bit more of a roadblock"

Orphanet rare disease biobanks per 100K of population



"With biobanking, we perform well in the Netherlands. However, it would also be beneficial if we would establish more registries"

Sources: Citeline| Trialtrove; Orphanet; Citeline Primary Research. Key players were interviewed for their insights, n=6

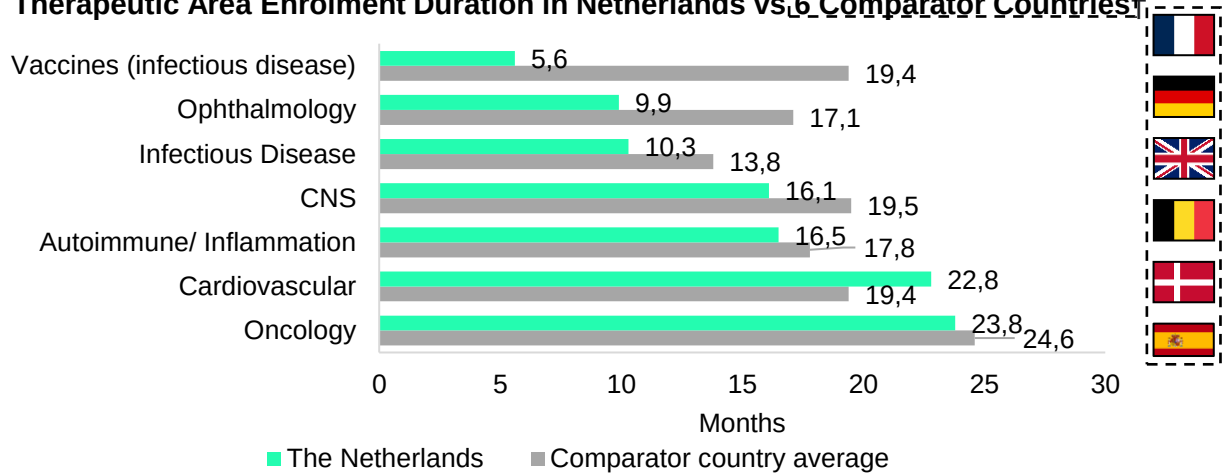
Therapeutic area specialism

The Netherlands offers unique opportunities for the enrolment of oncology clinical trials

Therapeutic area specialism

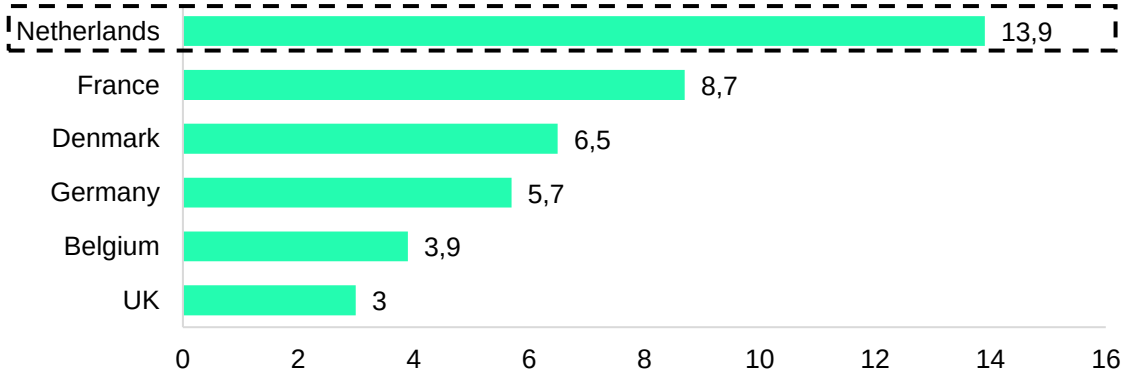
- The Netherlands has a shorter enrolment duration (time taken to enrol all patients onto a clinical trial) than the average of France, Germany, the UK, Belgium, & Denmark, across a broad range of therapeutic areas
- Therapeutic areas of note are:
  - **Oncology** – The Netherlands has shorter oncology enrolment durations than Belgium (34.1 months), Germany (25.8 months), the UK (25.5 months), and Spain (24.1 months)
    - ➢ The Princess Maxima Medical Centre in Utrecht is a collaboration bringing eight academic hospitals together into a single paediatric oncology centre, the largest in Europe
    - ➢ As of 2021, the centre employed over 900 healthcare employees, including over 400 scientists
  - **Cardiovascular** – The Netherlands has shorter cardiovascular enrolment durations than Denmark (25 months) and France (24.8 months)
    - ➢ The WCN & VRN cardiovascular KOL networks in the Netherlands have been cited as a critically valuable resource for those wishing to conduct cardiovascular research

Therapeutic Area Enrolment Duration in Netherlands vs 6 Comparator Countries†



†Single-country trials; All trial phases included; trial start dates 2018-2022; No COVID-19 trials

Oncology patients per 100K of population



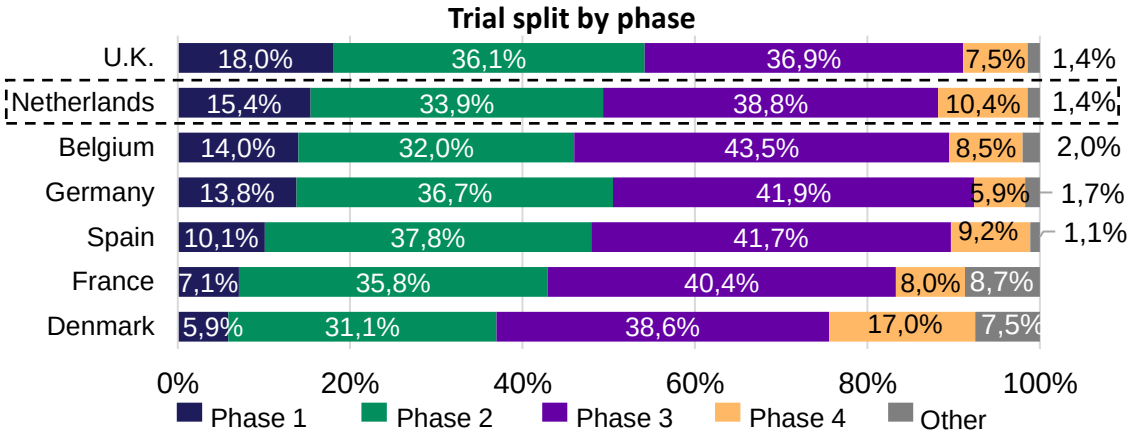
Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6

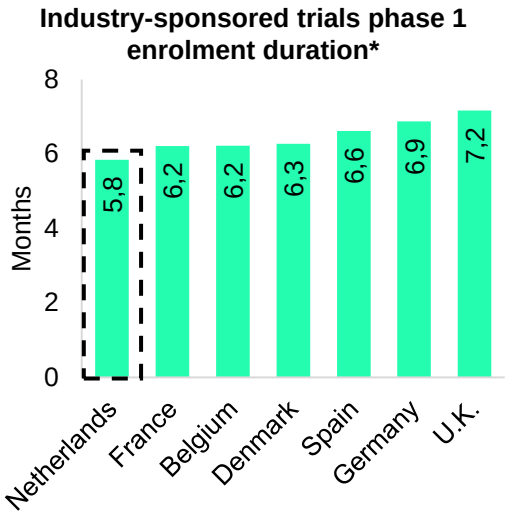
Early phase clinical trial specialism

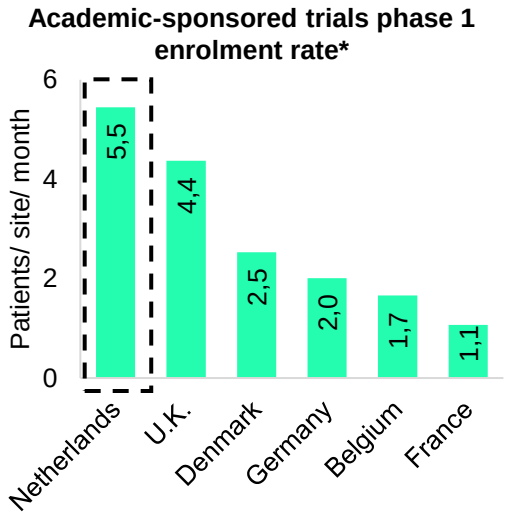
The Netherlands offers unique opportunities for the enrolment of early phase clinical trials

Early phase specialism

- The size and population density advantages of the Netherlands have already been established; these advantages are among the factors which result in the Netherlands having the fastest industry-sponsored trial enrolment duration and the fastest academic trial enrolment rates in certain phases
- The Netherlands has historically positioned its clinical trial split as having the 2nd highest proportion of phase 1 trials among the comparator countries
    - These early phase trials require fewer patients than later phases and are well suited to the Netherlands' smaller population
- **Industry-sponsored trials:**
    - Phase 1 – The Netherlands leads with an average enrolment duration of 5.8 months*
    - Phase 4 – The Netherlands leads with an average enrolment duration of 7.8 months*
- **Academic-sponsored trials:**
    - Phase 1 – The Netherlands leads with an average enrolment rate of 5.5 patients/site/months*





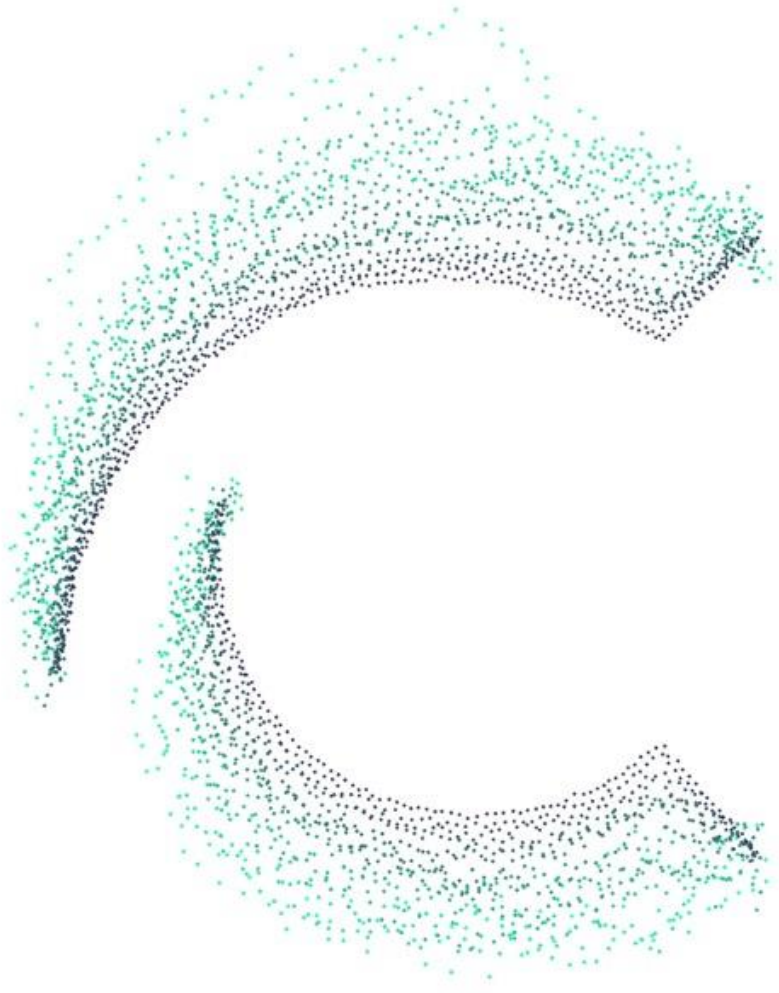


*Single-country trials initiated between 2018-22; no COVID-19 trials

Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6

CITELINE

3.5 Key figures on infrastructure for clinical research



The Netherlands is ranked 11th globally for both public health measures and healthcare system quality and has seen a rise in recent years of R&D and healthcare expenditure. Access to trial infrastructure and resources is high; on average there is 1 hospital within 5km across the country, and the number of physicians per 10,000 has been increasing over the years, below only Germany and Denmark of the comparator EU countries.

ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

R&D intensity and health expenditure

A rise in R&D and healthcare expenditure, particularly between 2019 and 2021, suggests investment in future innovation and quality of services

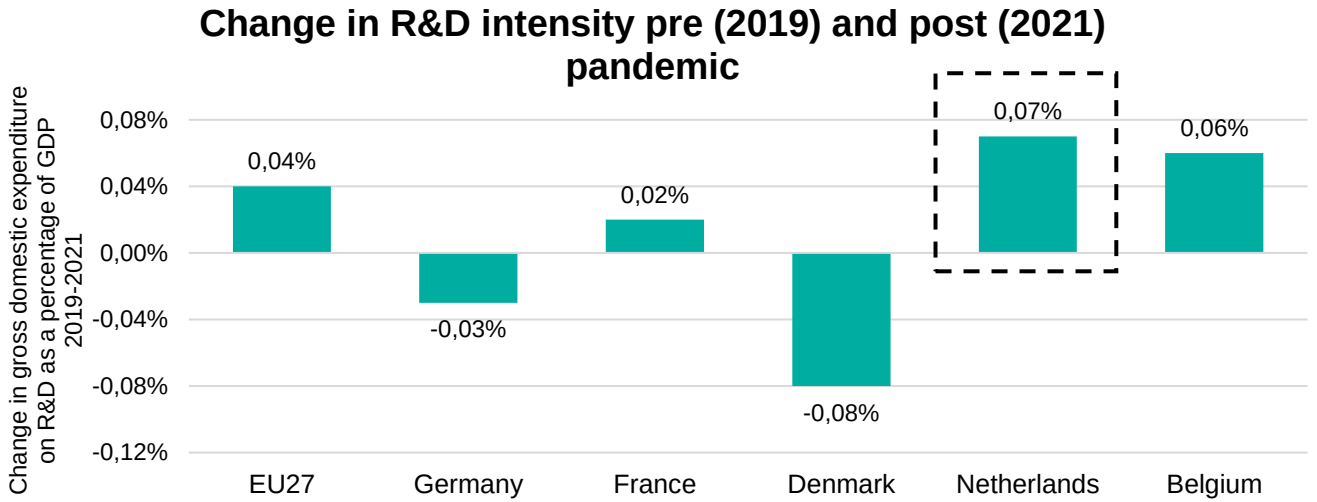
R&D intensity

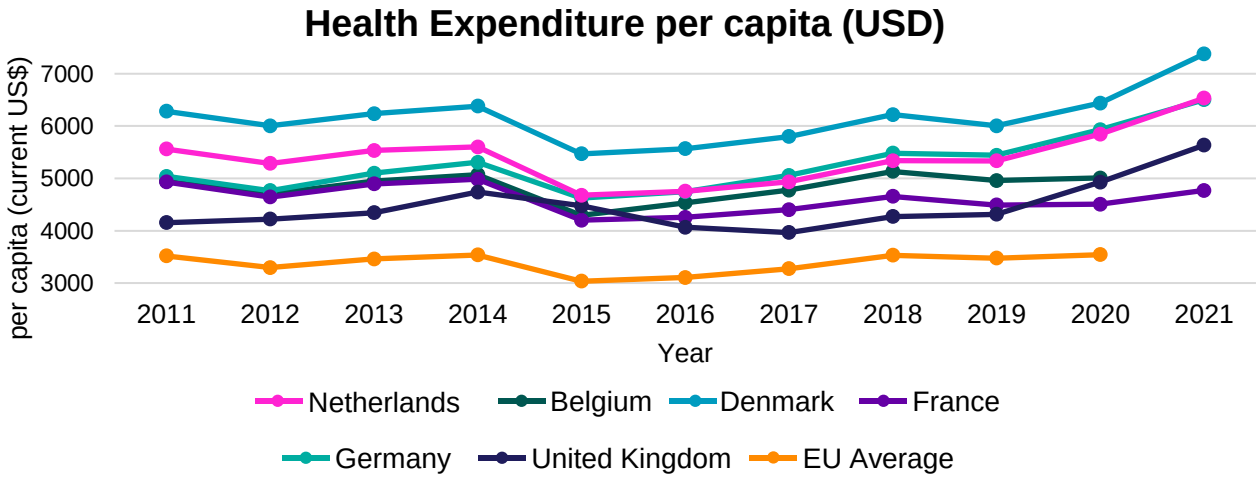
Between 2019 and 2021, the Netherlands has seen the greatest increase in science and technology R&D intensity compared not only with specific comparator countries, but also with the average across 27 EU countries. Of course, the response to the COVID pandemic will play a part in the figures within this year range.

In terms of sponsor trial budget allocation, in a series of interviews conducted by Citeline with six key players, it was found that pharma companies allocate substantially more budget to multinational trials than to single-country trials.

Health expenditure

Per-capita health expenditure has been on the rise in the Netherlands since 2015. The more pronounced uptick between 2019 and 2021 mirrors the trend seen in R&D spending.





Sources: OECD R&D intensity; World Bank; Citeline Primary Research. Key players were interviewed for their insights, n=6

Global healthcare rankings

The Netherlands is ranked 11th in the world both in terms of public health and healthcare system quality

Rank	Public Health Ranking, 2023	Healthcare Index Ranking, 2021
1	Singapore	South Korea
2	Japan	Taiwan
3	South Korea	Denmark
4	Taiwan, China	Austria
5	China	Japan
6	Israel	Australia
7	Norway	France
8	Iceland	Spain
9	Sweden	Belgium
10	Switzerland	United Kingdom
11	**Netherlands**	**Netherlands**
12	Luxembourg	Finland
13	Germany	Thailand
14	Hong Kong	Czech Republic
15	Finland	Norway

= European country

The Netherlands is ranked in the:

- **Top 15** countries **globally** both in a ranking of public health, and on healthcare system quality
- **Top 5 European** countries for public health
- **Top 10 European** countries for healthcare system quality

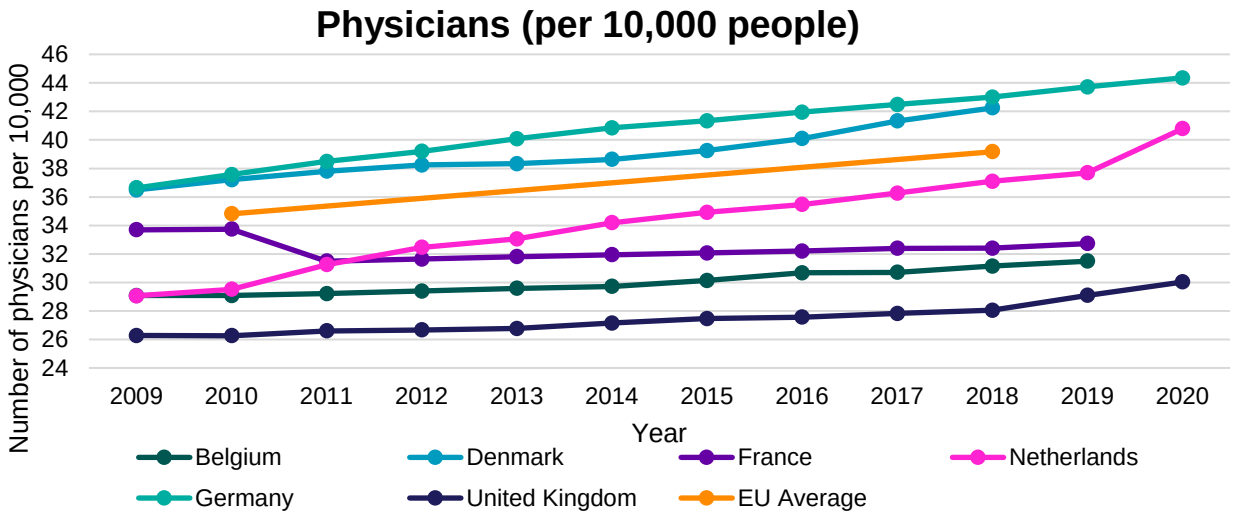
The rankings for public health are measured through the Legatum Prosperity Index “Health” pillar. This takes into account several metrics relating to the extent to which people are healthy and have access to necessary services to maintain good health. Factors contributing to the Netherlands’ high ranking include preventative interventions (immunization), care system factors such as satisfaction with healthcare, longevity (mortality rates), and emotional wellbeing.

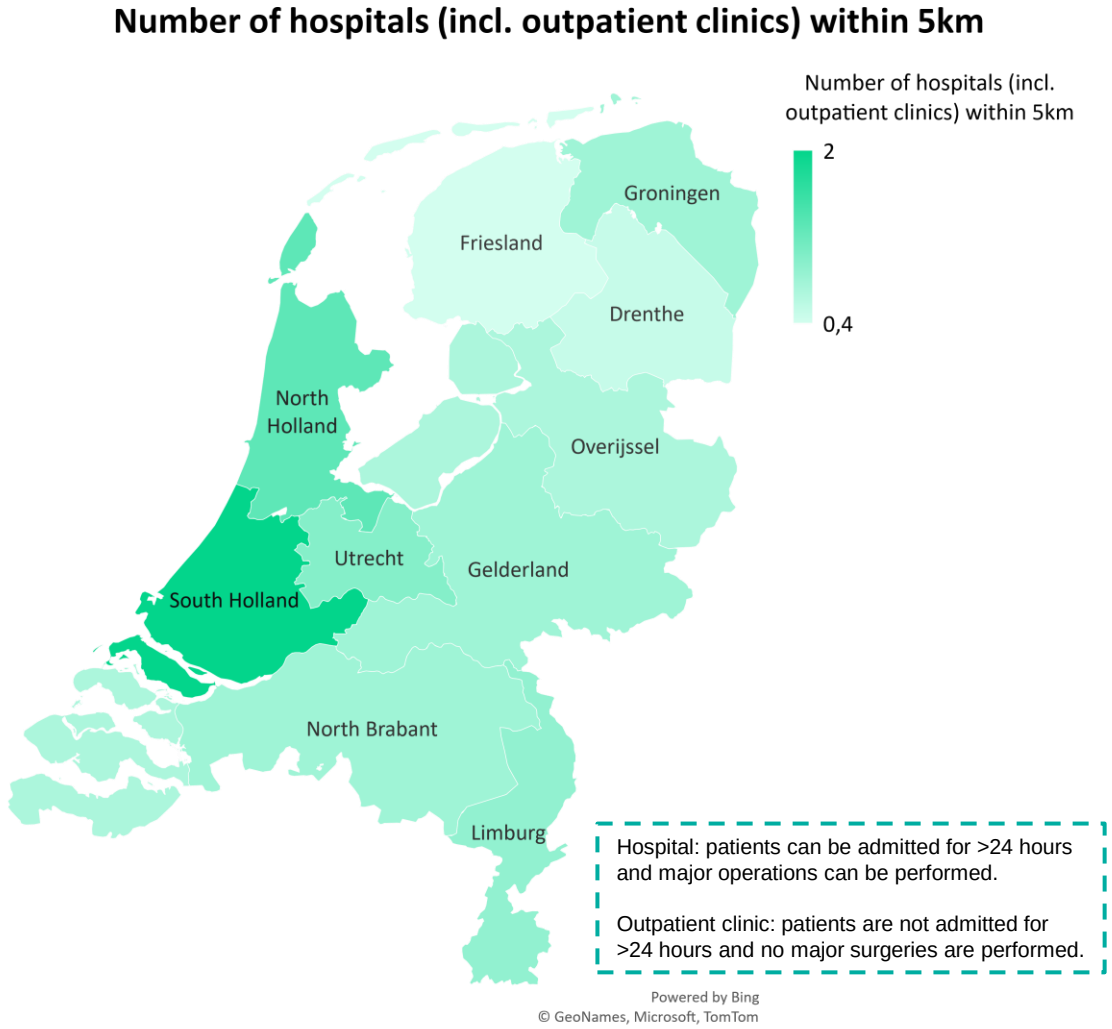
The rankings for healthcare systems are measured through the Health Care Index by CEOWORLD, which analyses the overall quality of the healthcare system. Factors contributing to the Netherlands’ high ranking include government readiness and infrastructure.

Sources: The Legatum Prosperity Index; Legatum Prosperity Index Methodology; CEOWORLD

Availability of hospitals and medical expertise

A high number of physicians per capita and high density of hospitals, particularly in the Randstad region, facilitates the logistics of running clinical trials in the Netherlands





On average there is 1 hospital (including outpatient clinics) within 5km in the entire country, with a larger density in the Randstad region, which encompasses Utrecht, Flevoland, North- and South-Holland. The number of physicians per 10,000 people has been growing over the years in the Netherlands, behind only Germany and Denmark within the set of comparator EU countries.

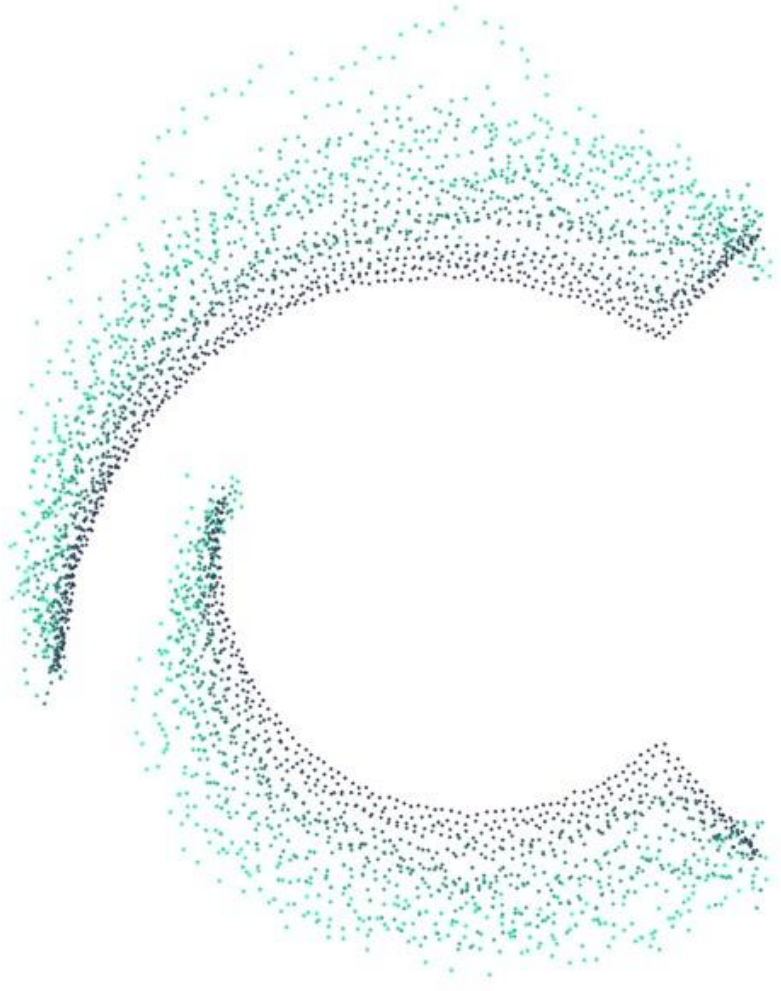
Proximity to both hospitals (particularly in the Randstad region) and a high density of medical expertise can facilitate the conduct of clinical trials, reducing time for patients to travel and access important clinical trial resources

Sources: Statistics Netherlands; World Bank

CITELINE

4. SWOT analysis of the Dutch clinical ecosystem

Strengths are seen for the Netherlands in research and innovation, stakeholder communication, and population density. Opportunities include a reduction in bureaucracy in academia and investment in patient cohort modelling. However, further action is needed to prevent shortfalls in trial personnel and to improve patient perceptions of industry-sponsored trials.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

SWOT analysis of the clinical trial ecosystem in the Netherlands

	Strengths	Opportunities	Weaknesses	Threats
General	• High quality phase 1 institutes • Attractiveness for ATMP trials	• Promote expertise in ATMP • Reduced dependence on CROs if the Netherlands can adopt chain integration	• Lengthy contracting and recruitment difficulties • Shortage of experienced ATMP professionals • Expensive to host trials	• Potential overburdening of academic hospitals • Extra internal steps at academic hospitals • EUCTR causing delays
Academic excellence	• High-quality scientific community with great presence in papers • Collaboration between academic centres and networks	• Using good communication of scientific experts to strengthen industry collaboration • Reducing the bureaucracy in academia could allow academic to focus more on innovation	• Limited numbers of academic sites means that, largely for early-stage trials, industry is often competing with academia for these sites	• Potential shortage of nurse practitioners on wards
Ease of conducting clinical trials	• Accessibility to academic hospitals • Responsiveness of Dutch stakeholders in set-up phase • Accessibility of regulatory agencies & patient groups	• Extremely fast CTA execution at phase 1 oncology centres • Reputation for timeline adherence • Improve patient perspective on industry to leverage the mutual goals the two stakeholders have in developing therapies	• Separate departments for pharmacy and investigator contracting • Hospital sub-departments having weigh-in slows approval process	• Insufficient personnel for contracting • Barriers to public-private collaboration due to different internal processes. • Scientific leaders remaining too Netherlands-focussed
Availability of patients	• Dense population • Concentration of patient populations into centralised locations	• Promote expertise in recruiting oncology & rare disease patients • Combine & centralise patient data sets	• Lack of a national electronic health record system vs competitors (e.g., Belgium) • Low public awareness of clinical trials	• Competition for patients at same hospitals • Negative attitude towards pharma makes industry trials less attractive
Future considerations	• Genetic research at academic hospitals • Early-phase rare disease trials	• Founder mutations for rare disease trials • More niche & personalised medicine trials • Strong presence in oncology, cardiology & CNS	• Small population size makes the country an inappropriate location for single country trials	• Communication between GPs and hospital records • Availability of professionals • Bureaucracy within hospitals • Lack of collaboration

SWOT analysis – academic excellence (1/2)

The Netherlands' academic strengths are its scientific output, researcher quality, and academic networks; top Dutch universities strengthen its position among the top 100 in Europe for clinical and life science research

Strengths

Scientific Output

- According to the European Innovation Scoreboard 2022, the Netherlands outperforms the EU average by 129% and leads in innovation
- The Netherlands takes the lead for scientific papers in the top 10% most cited worldwide. The country also ranks 2nd in the EU for the attractiveness of its research systems, which measures the international competitiveness of the science base
- The country ranks 4th in Europe according to SCImago's scholarly H-index ranking, excelling in fields like Rheumatology and Geriatrics

Researchers and Investigators

- In 2022, researchers in the Netherlands ranked 7th globally in the Clarivate Highly Cited Researchers analysis, demonstrating significant influence in the global scientific community

Academic Network

- Key players interviewed by Citeline noted that collaborating with Dutch academics is notably faster than in comparable EU countries
- The Netherlands has a robust network of research groups, such as WCN and VRN

Institutions

- All leading Dutch universities are in the EU's top 100 for clinical, preclinical, and health research and life sciences research

Source: European Innovation Scoreboard 2022; Times Higher Education; Scimago Institutions Ranking; Clarivate; Citeline Primary Research. Key players were interviewed for their insights, n=6

SWOT analysis – academic excellence (2/2)

Addressing knowledge gaps and reducing bureaucracy and resource shortages can boost collaboration and innovation

Weaknesses

- According to the OECD Skills Need Indicator, the Netherlands has the second highest shortage of scientific knowledge compared with other EU countries

Opportunities

- Short lines of communication among academics present an opportunity for the Netherlands to enhance its industry collaboration
- Reducing the bureaucracy in academia could allow academia to focus more on innovation

Threats

- One key player interviewed by Citeline stated that more nursing traineeships were required due to a shortage of nurses on the wards
- Key players also highlighted that the lack of availability of professionals would be a future bottleneck

Source: European Innovation Scoreboard 2022; Times Higher Education; Scimago Institutions Ranking; Clarivate; OECD; Citeline Primary Research. Key players were interviewed for their insights, n=6

SWOT analysis – ease of conducting clinical trials (1/2)

Easy access to stakeholders facilitated by a broad landscape of research networks makes collaboration easy; however, there are few Dutch-owned CROs in the Good Clinical Practice Network

Strengths

- Clinical trial stakeholders are easy to access, receive feedback from and are open for collaboration
- Clinical trial start-up timings in the Netherlands are competitive, particularly when considering time to first patient dosed, and phase 1 and 2 trial enrolment
- High number of research networks

Weaknesses

- Regarding stakeholder engagement:
  - Patients have low awareness of clinical trials and are wary of industry sponsorship due to mistrust
  - Increased communication with regulators required, and better alignment with developers
- Cost of clinical trial start-up can create a bottleneck – greater transparency is needed at an earlier stage on what the costs for sponsors will be, or standardising the expected trial site cost of assessments on a national level
- The issue of low population size is exacerbated when sites run too many competing studies, hindering enrolment
- Key players consider CROs to be of high importance in the Netherlands; however, of the 29 CROs in the GCP network in the Netherlands, only 24% are Dutch companies

Sources: Good Clinical Practice Network

SWOT analysis – ease of conducting clinical trials (2/2)

ATMPs is an area that the Netherlands could promote as a strength compared with other countries; however, access to those products still needs to be improved

Opportunities

- Despite ECTR harmonisation, the Netherlands can excel by expediting ethics approval and collaborating with other countries
- The Netherlands could stand out in ATMP trials by promoting speed in approvals and its high trial count relative to population size
- Investment in more innovative tools and models using historic data could help calculate realistic patient cohort sizes and assist trial recruitment
- Relative to comparator countries, the Netherlands has the highest proportion of planned decentralized trials, although key players are skeptical of their adoption

Threats

- The Netherlands has a relatively high number of ATMP trials relative to population size, but hindrances to access, such as the sluis list, could pose a barrier to high-cost ATMP use
    - Of the 21 products in the lock as of February 2022, 12 (57%) were orphans

Sources: Citeline| Trialtrove; World Bank; Xcenda

SWOT analysis – availability of patients (1/2)

The Netherlands is faster at enrolling trials across a broad range of indications vs. the comparator country average and scores highly in healthcare literacy; however, public education can be improved further

Strengths

- The Netherlands has the shortest enrolment duration for phase 1 and phase 4 industry-sponsored trials, and the fastest enrolment rate for phase 1 academic-sponsored trials*
- The dense population in the Netherlands ensures patients can commute to virtually any hospital in the country
- Concentration of patient populations into centralised locations
- The Netherlands offers specific advantages for rare disease and oncology trials
- Abundance of patient associations

*Single-country trials initiated between 2018-22; no COVID-19 trials

Weaknesses

- Lack of a refined national electronic health record system vs competitors (e.g. Belgium)
- Perceived low public awareness of clinical trials
    - The Netherlands ranks high for healthcare literacy but key players felt that further public education is needed on clinical trials
- Low population size limits patient reach and intensifies competition, especially in high-patient-count trials demonstrated through slow academic-sponsored trial enrolment rates and durations at phase 4

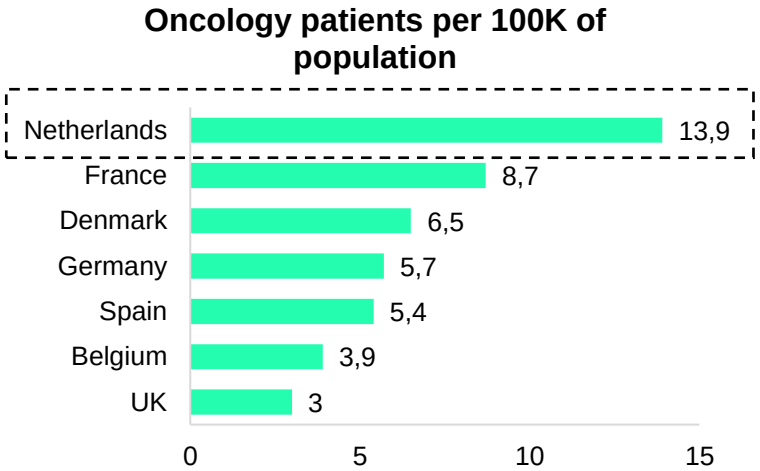
Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6; The Economist Intelligence Unit, Health literacy around the world, 2021; Pelikan et al., Measuring health literacy in Europe: Introducing the European Health Literacy Survey Questionnaire (HLS-EU-Q)

SWOT analysis – availability of patients (2/2)

The Netherlands is well positioned to recruit patients into early phase oncology trials (particularly in the paediatric setting); however, obstacles exist with national data infrastructure and patient attitudes

Opportunities

- Highlight existing infrastructure in paediatric oncology recruitment
- Access to academic hospitals results in fastest enrolment rate among select European competition*
- Highlight presence of founder populations within rare diseases
  - Sanfillipo disease & juvenile neuronal ceroid lipofuscinosis
- Technology is well leveraged in the Netherlands to facilitate ease of access to patients



*Single-country trials initiated between 2018-22; no COVID-19 trials

Threats

- Competition for limited patient pools at intra- and inter-hospital level
  - Limits the count of trials that can be efficiently enrolled
  - Country is better suited for recruiting phase 1 studies with reduced patient requirements – ranks 2nd place, behind the UK, for the proportion of phase 1 trials initiated between 2018-2022 (15.4%)
- Challenging attitude from patients towards pharma makes industry trials harder to recruit

Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6; Zeegers et al, Founder mutations among the Dutch, 2004

SWOT analysis – infrastructure for clinical research (1/2)

Proximity to hospitals and high number of physicians for the population size is an advantage for patients regarding access to trial infrastructure and resource; however, there are limited numbers of trial sites

Strengths

- With an average of 1 hospital within 5km across the Netherlands, and with the number of physicians per 10,000 people on the rise, access to clinical trial resources and medical expertise is high
- A global ranking of 11th in the world for public health and healthcare system quality positions the Netherlands highly as a reliable source of clinical trial resource

Weaknesses

- The Netherlands' small size results in fewer clinical trial sites, especially academic ones
  - Consequently, industry frequently competes with academia for these sites, particularly in early-stage trials
  - Currently, most trials sites are based in Amsterdam where there is a large patient population

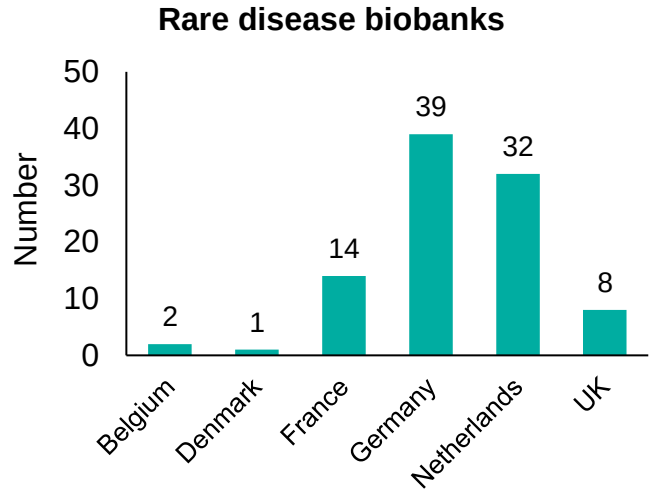
Sources: World Bank; Citeline| Sitetrove

SWOT analysis – infrastructure for clinical research (2/2)

Investment in R&D and the healthcare system has been on the rise in recent years and collation of patient data in the form of biobanks exceeds that of comparator countries, but more patient registries could be invested in

Opportunities

- Spending on health and R&D (as a percentage of GDP and per capita, respectively) was on the rise from 2019-2021
- The Netherlands is already strong in the collation of patient data in biobanks per capita and leads among comparators, with 0.18 *Orphanet* biobanks per 100K of the population. However, there remains the opportunity to build on this and excel further by establishing more patient registries



Threats

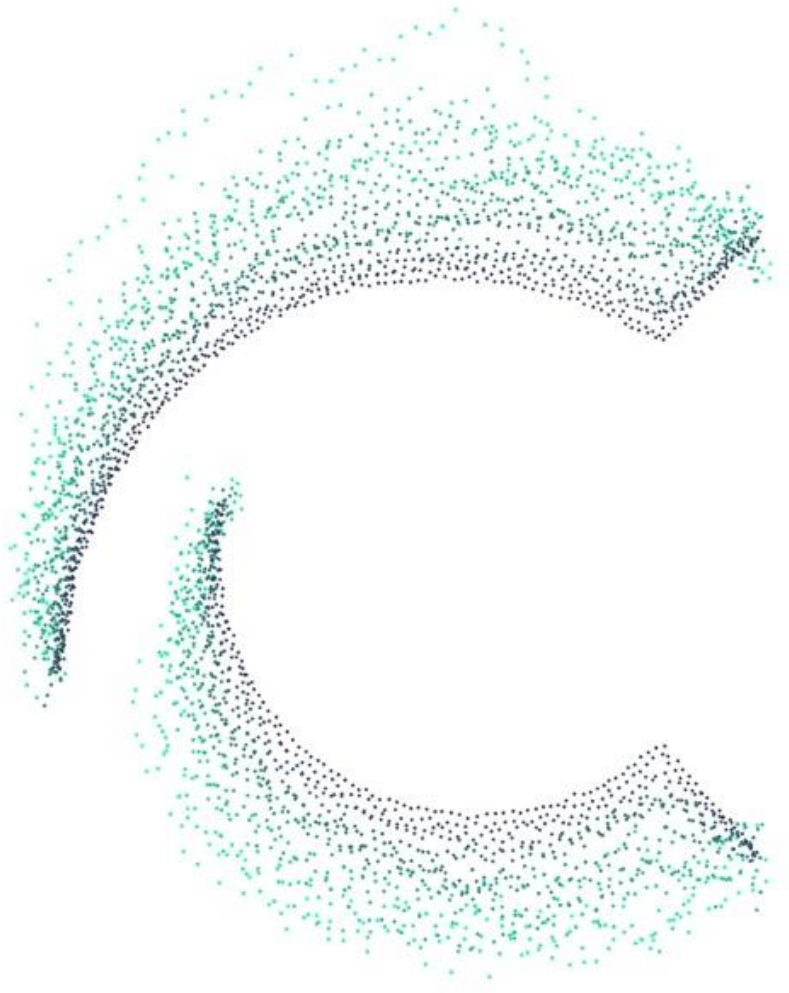
- Although investment into R&D and healthcare infrastructure is high, the number of hospital beds has consistently been below the EU average and is on a decline, which could impact availability for trials requiring overnight stays

Sources: Orphanet; World Bank

CITELINE

5. Netherlands comparison with Europe and advantageous key factors

The Netherlands offers advantages over other European countries in a range of areas, including a greater reputation for academic excellence, a high level of doctors and researchers per capita, faster ATMP clinical trial approval timelines, and short early phase trial enrolment durations.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Key comparisons within Europe

On a European and global scale, the Netherlands has proven itself as a hub of academic excellence with an abundance of innovative and highly cited researchers, supported by top-tier research institutes

Academic excellence

The Netherlands has the greatest proportion of its publications occupying the top 10% most cited worldwide and ranks 2nd in Europe as an 'Innovation Leader' for the attractiveness of its research systems as per the European Innovation Scoreboard (EIS). According to EIS, the Netherlands is an Innovation Leader, outperforming the EU average by 129%.

The Netherlands ranked 3rd in Europe and 7th globally for highly cited researchers in 2022. These researchers account for 2.9% of the global share of highly cited researchers, putting the Netherlands ahead of France (8th) and Switzerland (9th).

The Netherlands has more researchers per 1000 people employed than the EU average (~11 vs ~9). In the most recent figures, the Netherlands is also ahead of geographically larger competitors Germany (~10) and the UK (~10).

100% of the Netherlands' top 10 institutes for clinical, preclinical & health research have scored in the EU top 100. This same proportion is seen for the country's 7 assessed life science research institutes. In Belgium, Denmark, and France the proportion of each country's respective clinical, preclinical & health research institutes that are in the EU top 100 ranges from 67%-30%.

Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6

Key comparisons within Europe

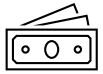
The Netherlands' openness to collaboration and ease of access to trial stakeholders facilitates efficient trial set-up and conduct, exemplified by the joint-fastest ATMP trial approval times in Europe

Ease of conducting trials

The Netherlands is competitive in clinical trial start-up timing. In 2020, the time between trial application and first patient dosed was similar for Germany (226 days), the Netherlands (229 days), and the UK (247 days). France had the longest timeline at 266 days. The opportunity is stronger for ATMP trials; the Netherlands is one of just two countries (the other being the UK) that have approved ATMP trials in less than 30 days.

Early-stage trial recruitment is where the Netherlands stands out among comparator EU countries. For phase 1 and 2 trials, the enrollment duration in the Netherlands is below the European average for these phases. The enrolment rate for the Netherlands is the fastest for industry-sponsored trials, having the joint second-fastest rate alongside the UK, behind Germany. The Netherlands also has the joint fastest enrolment rate for joint academic and industry trials but is second slowest for academic studies alongside France and Belgium. France benefits from a standard mandated template agreement for clinical trials ("Convention Unique"), Belgium launched a campaign to encourage trial recruitment in 2017, and Denmark has a free service (Trial Nation) to help with study start-up.

The Netherlands is a member of the Scientific National Advice Service pilot launched by the EU-innovation Network. This pilot is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously. Belgium, Denmark, France, and Germany are also members.



Fees for scientific advice range from around 6,860 to 15,650 EUR, placing the Netherlands in the mid range compared with other EU countries, as with clinical trial application costs. Germany and the UK, however, do offer some advice for free, and clinical trial applications are free in Belgium, while France charges no fees on both counts. Similarly to Belgium and the UK, the Netherlands does offer reduced rates for small companies and academics, primarily in early-stage development.

Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6

Key comparisons within Europe

The Netherlands offers unmatched advantages for patient availability: high population density, many biobanks, and efficient enrollment all contribute to easing access for patients

Availability of patients

The Netherlands has the highest population density in Europe (518 people per sq km), which is significantly more than the nearest competitor, Belgium (381 people per sq km). This population density, in combination with the high hospital density (1.1 hospitals, including outpatient clinics, within 5 km), enables a large pool of potential patients to quickly access available trials.

The Netherlands has the highest number of rare disease biobanks per 100K of the population (0.18), nearly 4x higher than the nearest competitor, Germany (0.05), and ahead of France (0.02), Belgium (0.02), Denmark (0.02), and the UK (0.01).

The Netherlands has a shorter enrolment duration (time taken to enroll all patients onto a clinical trial) than the combined average enrolment durations of France, Germany, the UK, Belgium, Denmark, and Spain. This advantage is seen across vaccines (infectious disease), ophthalmology, infectious disease, CNS, autoimmune, and oncology trials.

The Netherlands led between 2018-2022 for patients treated per 100,000 of the population in oncology trials (single-country trials) at 13.9; it is also competitive in CNS trials at 2nd most per 100,000, behind Denmark. At 23.8 months, the Netherlands has shorter oncology enrolment durations than Belgium (34.1 months), Germany (25.8 months), the UK (25.5 months), and Spain (24.1 months).

When evaluated by enrolment durations of single-country, non-COVID-19 trials, the Netherlands has the fastest durations for industry-sponsored phase 1 and phase 4 trials, at 5.8 and 7.8 months, respectively. For academic-sponsored trial enrolment rates over the same period, the Netherlands leads with 5.5 patients per site per month.

Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6

Key comparisons within Europe

The availability of patient data in biobanks for rare diseases is high, as is availability of medical expertise; the Netherlands has a strong record of investment in the healthcare system, with expenditure rising in recent years

Healthcare infrastructure

Similarly to Belgium and Germany, multiple health insurance funds or companies are the main sources of basic health coverage, with health insurance being mandatory, while free healthcare is available in Denmark and the UK. France and the UK both have highly centralised healthcare systems; the Netherlands has centralised institutional care, but municipalities have responsibilities in youth care, long-term care, and income support.

The Netherlands has the second highest number of rare disease biobanks, below only Germany, which has 7 more; however, the Netherlands has the third fewest number of rare disease patient registries with 42, above only Belgium (38) and Denmark (3).

Per capita health expenditure has been increasing in the Netherlands since 2015, and in recent figures, it was ~2x higher than the EU average. In 2021, the Netherlands spending was in 2nd place behind Denmark at $6531, compared with $7375.

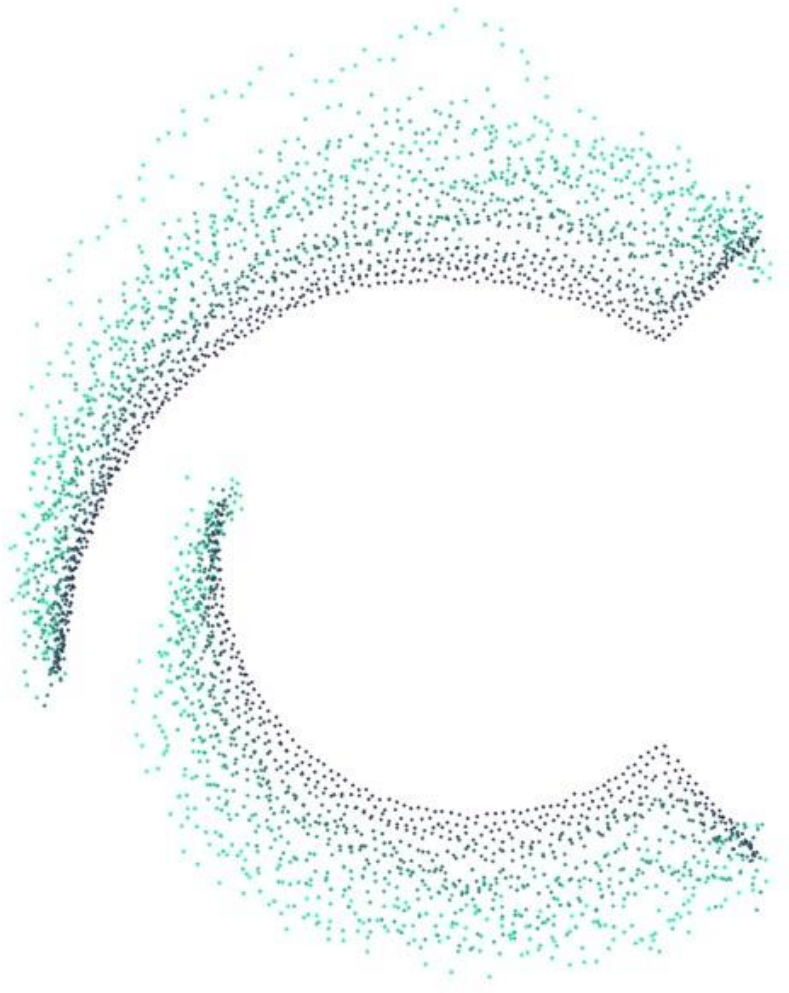
The Netherlands has ~41 doctors per 10,000 people, only narrowly behind Germany (~44) and Denmark (~42) and ahead of France (33), Belgium (32), and the U.K. (30). The high count of doctors per patient facilitates the logistics of running clinical trials in the Netherlands.

Sources: Citeline| Trialtrove; Citeline Primary Research. Key players were interviewed for their insights, n=6

CITELINE

6. Conclusion on clinical research areas where the Netherlands stands out

The Netherlands excels in several key areas, including efficient stakeholder communication, easy patient access to healthcare, high scientific research output, and the calibre of its researchers. The Netherlands has particular appeal in paediatric oncology and ATMP research.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Conclusion

With world-class universities, innovative ATMP efforts, and leading oncology research, the Netherlands excels in clinical research, backed by efficient networks, accessible healthcare, and governmental innovation support

The Netherlands stands out as a highly attractive hub for clinical research due to several compelling factors. The Netherlands' unique advantages include short communication lines among stakeholders, facilitating seamless and quick collaboration, and the country's dense population, which ensures that patients can easily access hospitals and sites across the country, enhancing the efficiency of clinical trials.

The Netherlands is a world leader in scientific research, as indicated by its position in highly cited scientific papers. The Dutch University Medical Centres serve as national hubs for rare disease expertise and are actively engaged in European Reference Networks. Also, all major Dutch universities rank in the European top 100 and rank second out of 28 European countries for the attractiveness of their research systems, emphasising their excellence in patient care, research, and education.

With efforts such as the Netherlands Centre for the Clinical Advancement of Stem Cell & Gene Therapies (NecstGen) and the development of a dedicated Core Facility in 2022, the Netherlands' commitment to advancing the field of ATMPs enhances the country's appeal.

The Netherlands excels in oncology studies, with shorter enrollment times than neighbouring countries. The Princess Maxima Medical Centre, Europe's largest paediatric cancer centre, exemplifies the Dutch commitment to collaboration and innovation, uniting eight academic hospitals with over 900 medical professionals. Additionally, the Netherlands leads in treating patients per 100,000 people in single-country cancer trials, showcasing its ability to conduct novel oncology research.

The Netherlands also has a plethora of patient associations and clinical research networks, such as WCN (Werkgroep Cardiologische Centra Nederland), a collaboration of 50+ cardiovascular investigators, and the Belgian Dutch Clinical Pathway Network, which has spearheaded over 1000 projects across 57 participating organisations. The Netherlands has strengthened its position as a top destination for clinical research by establishing such strong networks and collaborations.

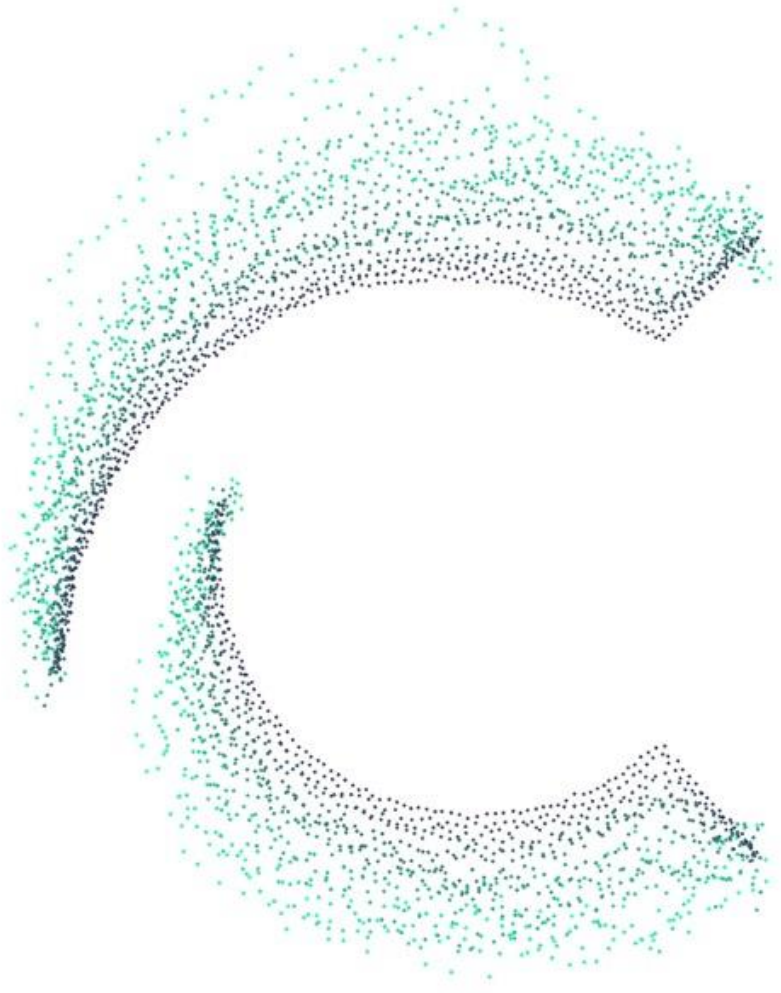
The Dutch government's commitment to supporting innovation, particularly in the life sciences and health sectors, further solidifies the Netherlands' position as an attractive environment for clinical research.

The combination of excellence in academia, ATMP and oncology expertise, and high-quality research and patient care ultimately enhances the country's status as a global clinical research leader.

CITELINE

7. Recommendations

To become more attractive for clinical research and excel on the global stage, the Netherlands must promote its expertise, expand its clinical research workforce, streamline approvals, improve reporting, boost public awareness, and foster greater collaboration. These strategic actions will fortify the Netherlands' position in clinical research.



ACRON ccmo DCRF Dutch Clinical Research Foundation FAST Health~Holland INVEST IN Holland Vereniging Innovatieve Geneesmiddelen

Recommendations (1/4)

To attract more clinical research to the country, the Netherlands needs to be vocal about its expertise to an international audience, while simultaneously increasing capacity in its clinical research workforce

1

Enhance the visibility of clinical research at international conferences and events

Despite its expertise in clinical research, especially in ATMP and early-phase studies, the Netherlands tends to be reserved about its accomplishments in these areas. During interviews with key players, the unanimous opinion was that the Netherlands is an attractive country for ATMP trials given its high expertise and innovation. However, the country has not fully harnessed its potential in promoting itself as a global leader in this area. Experts from the Netherlands are perceived as contributing less compared with their counterparts from other countries when it comes to participating in panel discussions and presenting at conferences.

To bridge this gap and maximise the potential of the Netherlands as a frontrunner in clinical research, it is imperative to encourage specialists to actively engage as panel participants and sponsors. This proactive involvement will result in mutual benefits: the Netherlands will be able to effectively position its clinical research expertise internationally, while experts will be able to expand their networks and gain exposure to new concepts and business practises, which they will be able to transfer back to the Netherlands.

2

Strengthen the clinical research workforce

The Government has listed life sciences as one of the nine innovative top sectors. To strengthen its international standing, the Netherlands needs proactive and direct efforts to build and train a larger skilled life sciences workforce. Interviews with key players revealed that insufficient availability of professionals could be a potential barrier to improving clinical attractiveness, especially for ATMP studies.

A strategic approach for the Netherlands could involve collaborating with prominent higher education institutions, particularly its esteemed University Medical Centres known for clinical research. The aim of this collaboration would be to encourage the cultivation of industry graduate roles such as clinical research associates, clinical trial coordinators, site activation specialists, and study feasibility experts.

More accessible scholarships and bursaries can incentivize students to pursue Master's and PhD programs, strengthening the future workforce. Investments in initiatives such as careers fairs and internships will further bridge the gap between academia and industry.

This strategic approach will not only contribute to a stronger workforce, but also showcase the Netherlands' academic excellence in the global landscape.

Source: Citeline Primary Research; Key players were interviewed for their insights, n=6

Recommendations (2/4)

Streamlining and improving the efficiency of contracting and trial approvals will strengthen the Netherland's attractiveness; the Netherlands could also explore establishing an open-access reporting database

3

Increase the efficiency of approvals and start-up times

During key player interviews, the need for the Netherlands to streamline contract execution and clinical trial approval was voiced repeatedly. With the implementation of the Clinical Trial Regulation, there is a greater emphasis on meeting delivery deadlines.

These key players advised that there was a need for minimising bureaucratic barriers within hospitals and academic institutions. Sponsors should also be encouraged to maintain direct and timely communication when operating in the Netherlands. Key players advise starting recruitment discussions as soon as possible and collaborating with experienced Contract Research Organisations (CROs). They believe that within ECTR there is room for the Netherlands to still stand out among other EU countries by, for example, focussing on faster ethics approval timeline at hospital level, and being flexible. Standardisation was also mentioned, including introducing a central template for clinical trial agreements, and standardising the expected trial site cost of assessments on a national level.

4

Improve reporting on clinical research

Clinical trial reporting is vital for industry sponsors selecting trial locations. Sponsors require data on a country's recruitment performance compared to global and national targets, as well as cost per patient for assessing cost-effectiveness. Unfortunately, there is a lack of information regarding actual trial participant numbers and trial time metrics in the Netherlands. Gathering this data would enable government and funding agencies to make more informed decisions about where to allocate resources for research and help inform recruitment efforts.

The Netherlands can expand on annual reporting and adopt a more comprehensive database dashboard. Spain's BEST Project is an exceptional example of a database platform used to report various aspects of clinical research. It includes the number of ethics committees and submissions, types of clinical research, and crucially, time and recruitment metrics. Implementing a similar platform can help streamline reporting and make it more comprehensive.

Also, with the Clinical Trials Regulation now requiring all information stored in the CTIS database to be publicly available, unless exempt, the CCMO can work on using the standardised reporting to create a comprehensive Netherlands-specific, open-access trial data dashboard.

Source: Medicamentos Innovadores, Citeline Primary Research; Key players were interviewed for their insights, n=6

Recommendations (3/4)

Efforts should be made to raise public awareness of clinical trials, as well as to increase academic hospital collaboration, such as by forming a National Life Science Council

5

Improve public perception of industry-sponsored trials

In terms of health literacy, the Netherlands stands out favourably in comparison with the European average, as indicated by the European Health Literacy Survey. In the Netherlands, 71% of respondents have 'sufficient' or 'excellent' general health literacy, surpassing the 53% average across eight EU countries. However, there is a need to bolster public perception of industry-sponsored clinical trials.

A concern raised by key players is the limited awareness of clinical trials in the Netherlands, leading to a perception of low clinical trial engagement in the Netherlands and causing the country to be overlooked as a go-to destination. Greater trial awareness may increase the proportion of the population that participates in trials. Sponsors should raise awareness and actively engage the public throughout the research process. This transparency cultivates a more positive public opinion.

The Netherlands benefits from easy access to patient advocacy groups, which are a pivotal avenue for raising awareness about the importance of clinical trials, educating communities, and dispelling misconceptions.

The CCMO should also continue to strengthen its efforts in its Patient Participation Programme to further bolster positive public opinion.

6

Encourage better collaboration between academic hospitals and industry sponsors

Key players pointed out challenges in collaboration between academic hospitals and industry sponsors. These challenges were said to stem from differences in internal processes between academic hospitals and sponsors. The barrier to collaboration with industry in the academia poses a barrier to public-private collaborations and to the access of biobank material.

Furthermore, within academic hospitals, it was noted by one key player that it can be difficult to get hospital boards to align.

To further strengthen knowledge sharing and dialogue between the public and private sectors, the Netherlands should consider adopting a similar approach to Denmark and establish a National Life Science Council comprised of representatives from companies, foundations, industry organisations, employee organisations, patient associations, universities, and representatives from the healthcare system.

Source: Strategy for Life Science Denmark, Citeline Primary Research; Key players were interviewed for their insights, n=6

Recommendations (4/4)

The Netherlands should create a centralised website where all research networks are listed and categorised by therapy area, services, partners and sponsor types

7

Create a comprehensive landing page where clinical research networks are categorised

There is a rich clinical research network within the Netherlands, fragmented by specialty. For example, WCN (Werkgroep Cardiologische Centra Nederland), is a network of cardiovascular investigators across 50+ institutions partnering with pharmaceutical companies, CROs, and academic organisations. Another example is the Belgian-Dutch Clinical Pathway Network (BDCPN), a network involved in over 1000 projects in 57 participating organisations across Belgium and the Netherlands that supports multi-centre research projects and international collaboration.

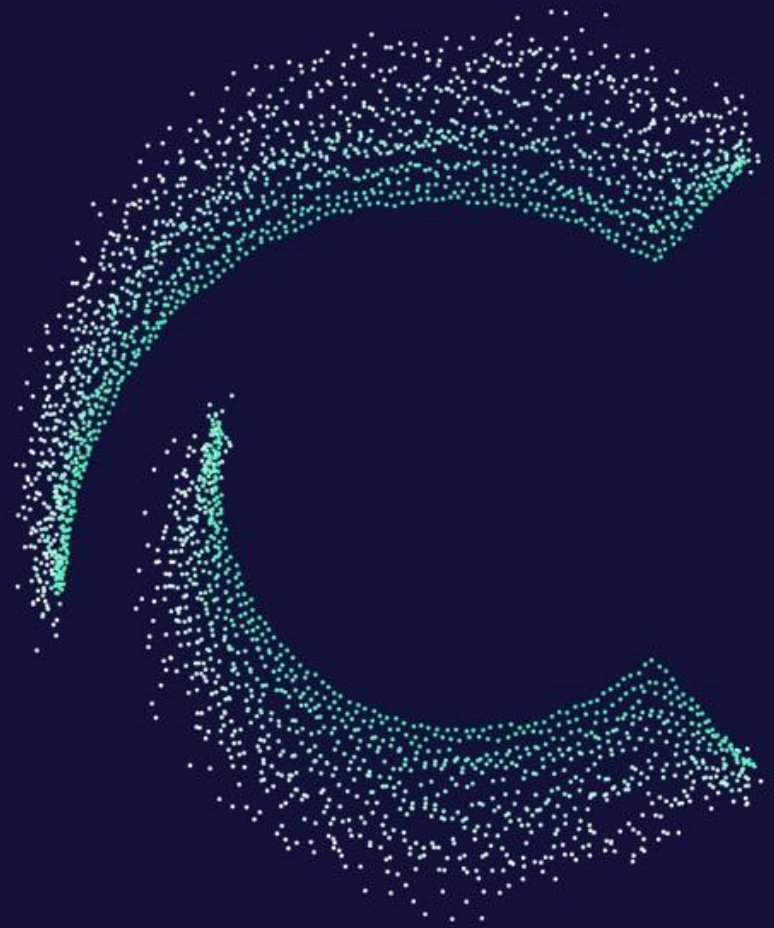
When it comes to oncology networks in the Netherlands, they are primarily structured by geographical regions. For instance, Oncomid operates in central Netherlands, OncoNoVo+ in the North Holland/Flevoland region, and OncoZon in the Southeast Netherlands region.

The proposal is to develop a comprehensive landing page that categorises these networks based on services, therapy areas, and sponsor types. This centralised hub will provide a more holistic view of all available research networks, facilitating knowledge sharing and enhancing collaborative efforts within the clinical research community.

Source: Citeline

CITELINE

Appendix



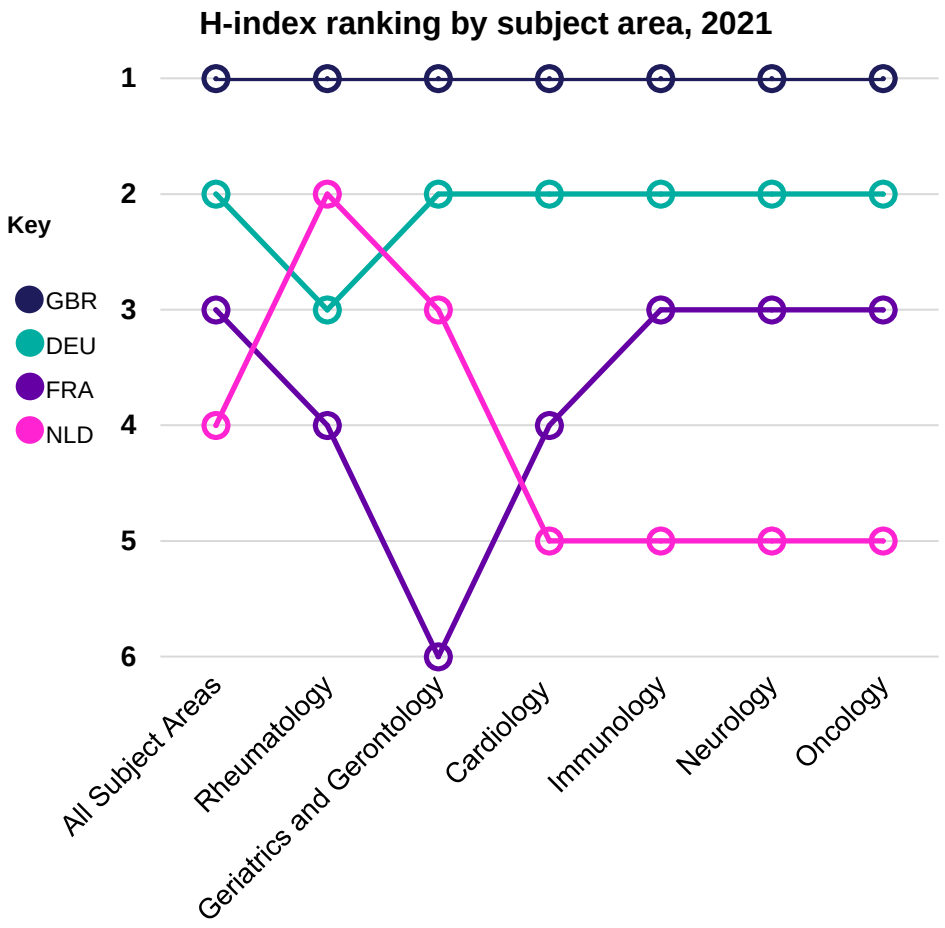
The Netherlands' government life sciences strategy

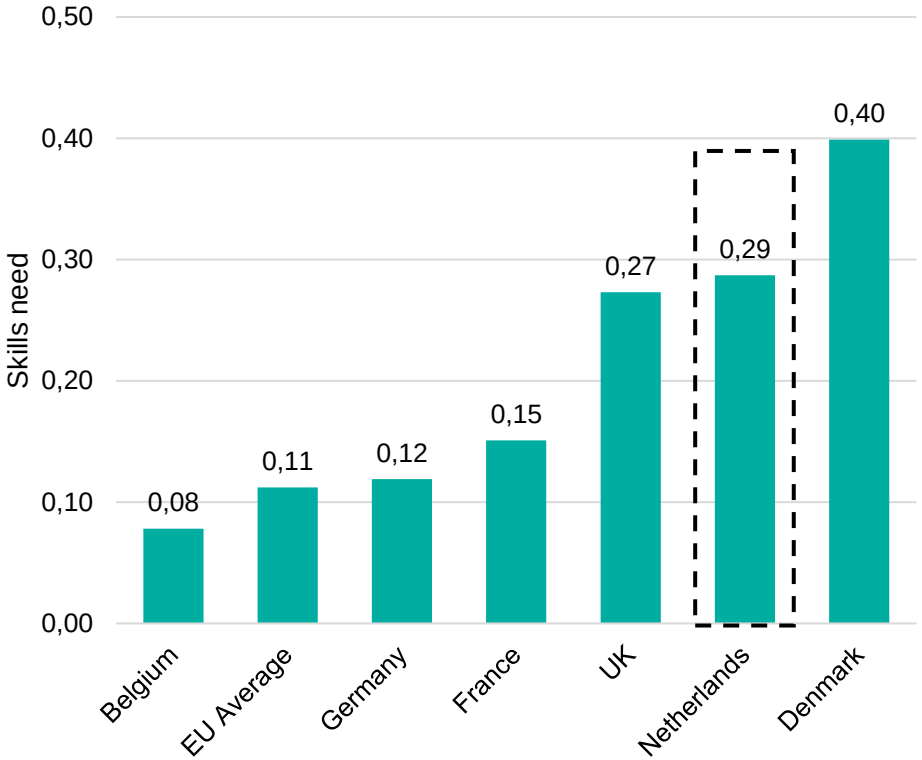
The Dutch Government is maintaining the country's focus on life sciences & health innovation via investment in near-term product development and is pushing for greater environmentally friendly processes

Collaboration across other EU countries	• Austria, Belgium, Ireland, Luxembourg and the Netherlands have joined forces in the BeNeLuxA initiative to give patients access to innovative medicines faster and at an affordable price
Boost sustainability in healthcare through Dutch Green Deal	• Committed to 5 main goals – focusing more on the health of patients and employees; increasing the awareness and knowledge of the healthcare sector's environmental impact; reducing CO2 emissions by 55% by 2030 with the goal of becoming carbon neutral by 2050; reducing the use of raw materials by 50% in 2030 compared to 2016; and reducing the environmental impact through medication usage
Focus on research for neglected diseases	• The Dutch Ministry of Foreign Affairs has awarded a €14m grant to support DNDi's objective to deliver 8 to 10 new treatments for poverty-related diseases, in particular illnesses that disproportionately impact and disadvantage women of childbearing age
Establishment of maximum price for medicines in the Netherlands	• The Dutch Medicine Prices Act sets maximum allowable prices for medicines in the Netherlands, based on the average cost of similar medicines in 4 reference countries. • The most recent price cuts for medicines have resulted in lower maximum prices, which secured estimated savings of over €100m in 2021 • High-cost innovative medicines are subject to the Lock procedure. Part of this procedure are price negotiations between government and company. Over the past 5 years, the Lock has resulted in savings of €1 billion.
Encouragement of enterprise and innovation in life science	• The Netherlands lists life sciences and health among their top nine sectors • In 2021 the government announced that €1.35 billion will be allocated from the National Growth Fund to projects relating to AI, regenerative medicine, health data, infrastructure, quantum technology and green chemistry • Part of this commitment includes the national icons competition, which selects Dutch products at the cutting edge of innovation (such as the Lighthouse by ASML for radiotherapy treatments)

Source: BeNeLuxA; Dutch Green Deal; DNDi; NL price & supply; National icons

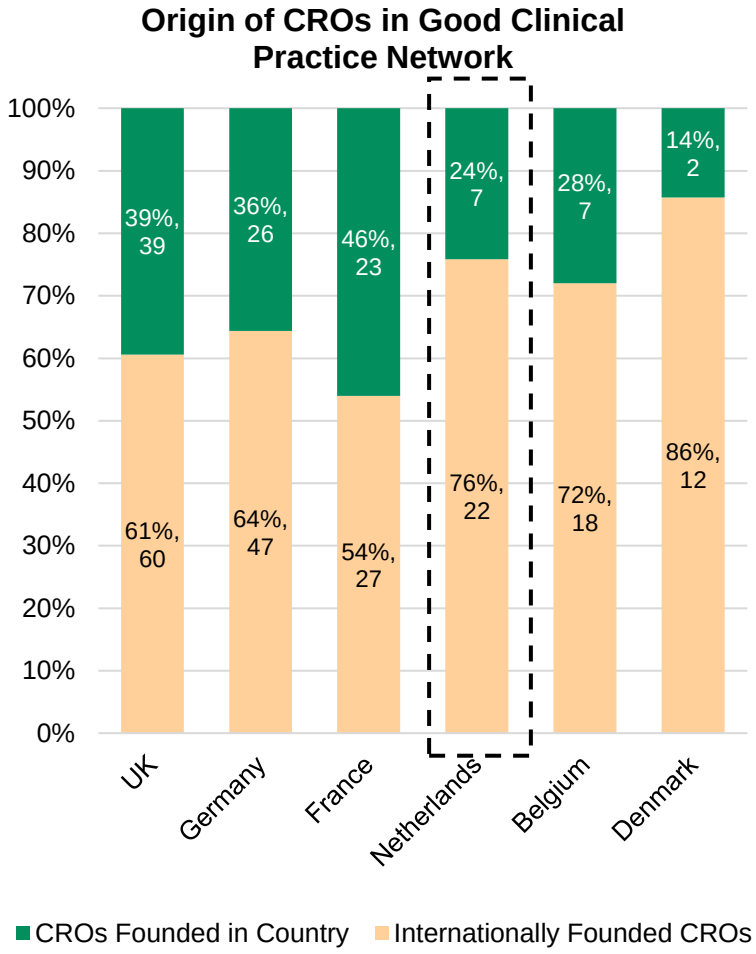
Key figures supporting SWOT analysis - academic excellence

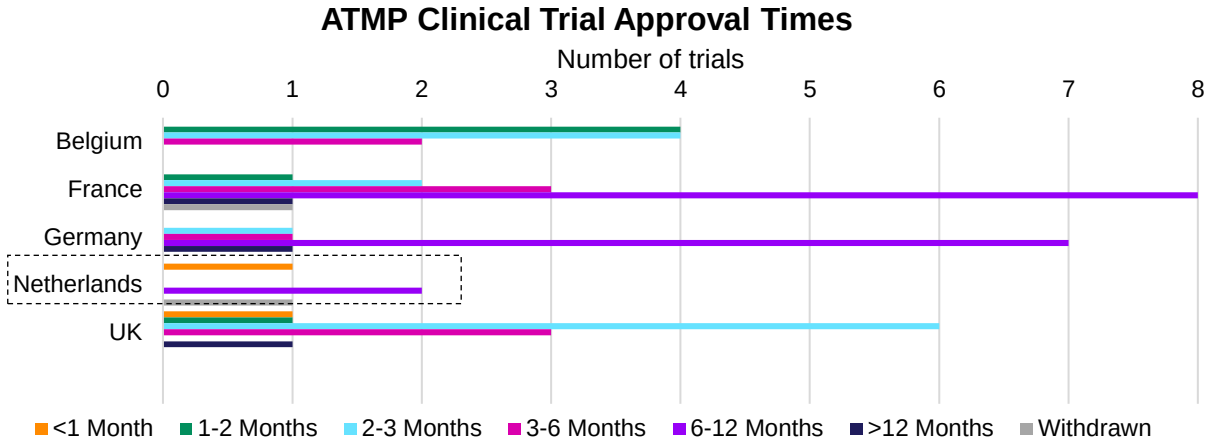


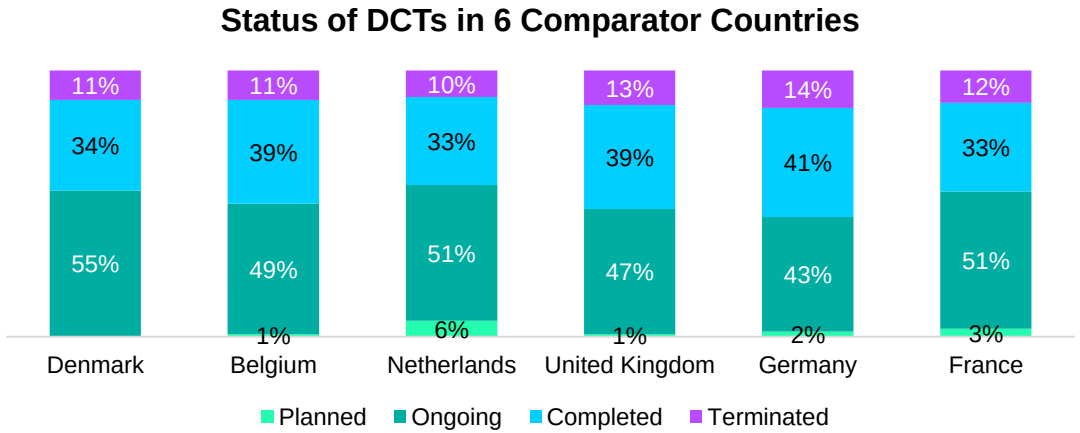


- The indicator was calculated by the OECD using data from the European Union Labour Force Survey
- Positive values indicate skill shortage (negative would indicate a surplus)
- The larger the absolute value, the larger the imbalance

Key figures supporting SWOT analysis - ease of conducting clinical trials

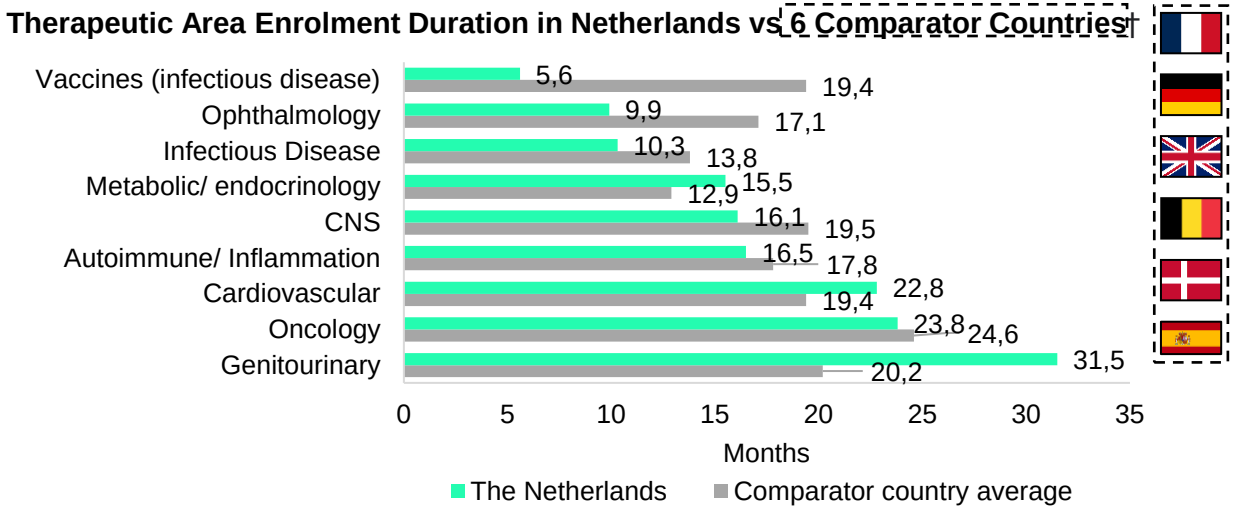


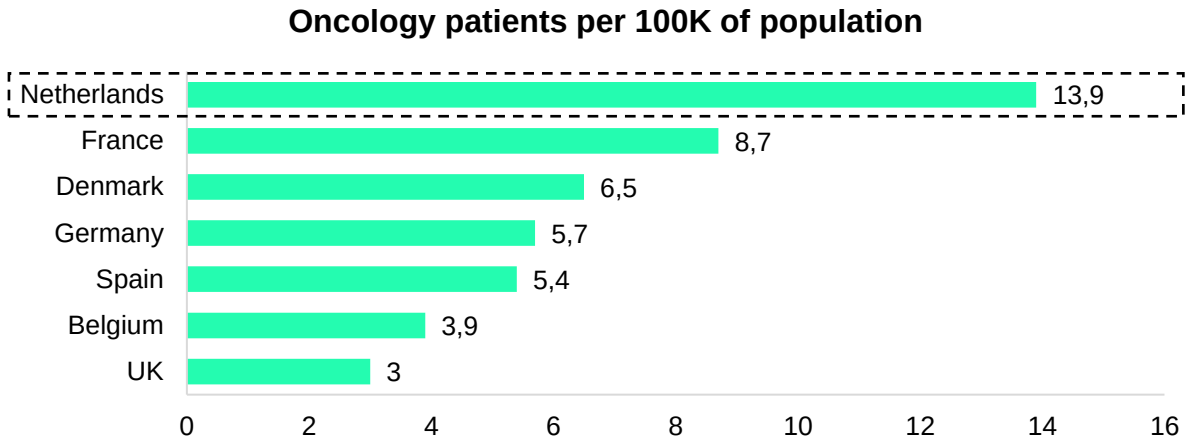


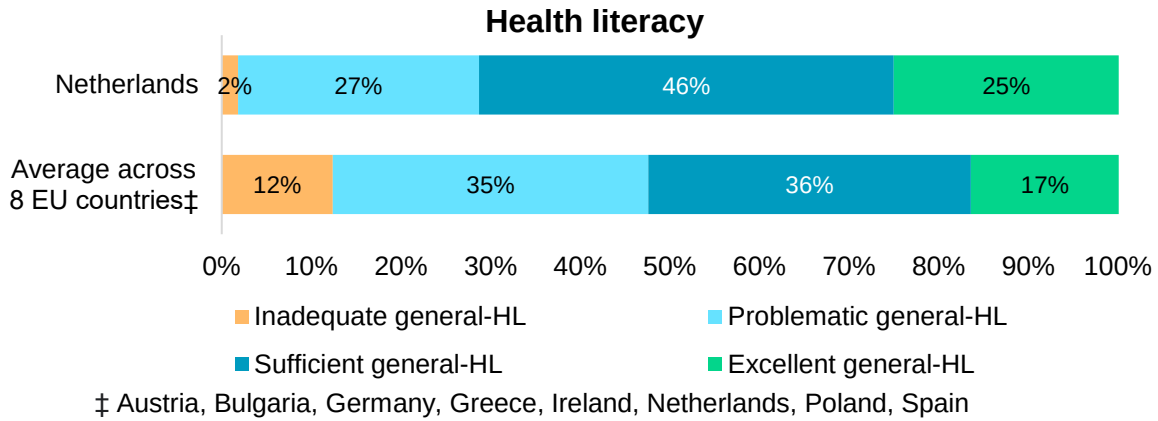


Inclusion Criteria: Trial Start Date: 01/01/2018-31/12/2022; Trial Status: Planned, Ongoing, Terminated, Completed. **Exclusion Criteria:** Study Keywords: NOT 'Observational' OR 'Non-interventional'

Key figures supporting SWOT analysis – availability of patients

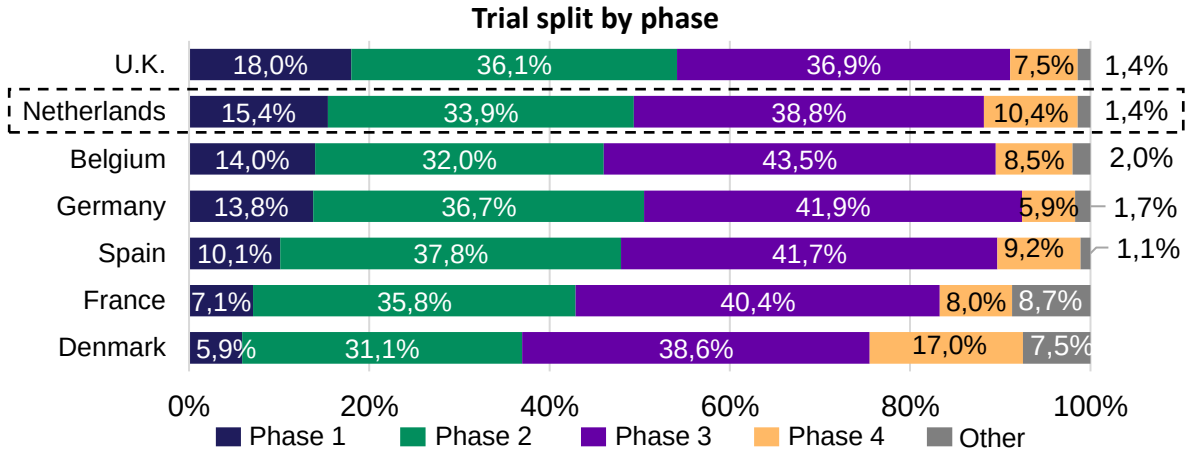




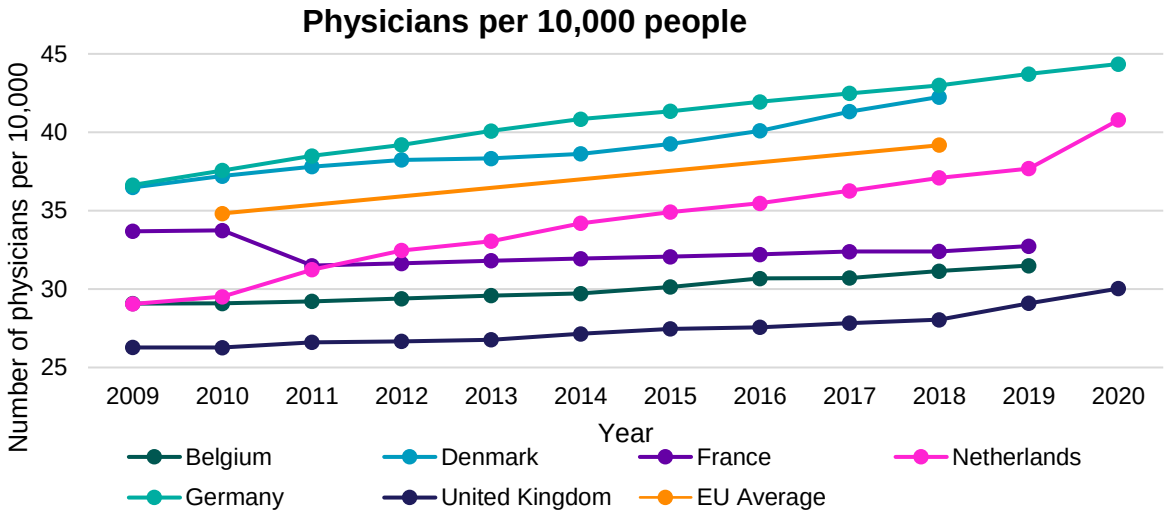


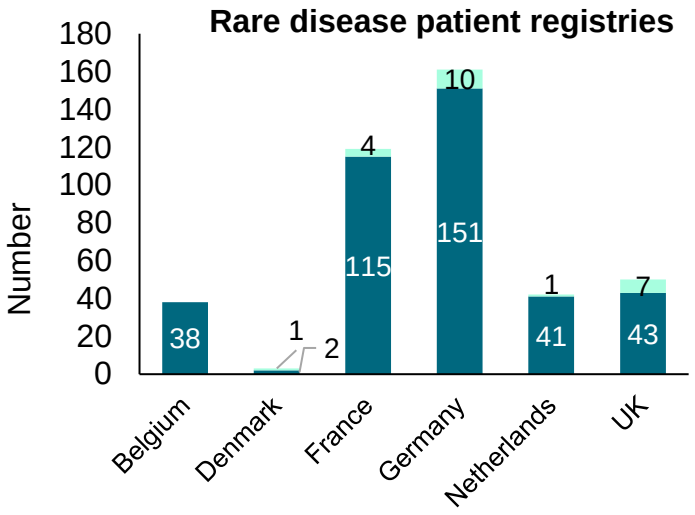
"In general, there's either ignorance or negative sentiments to clinical trials"

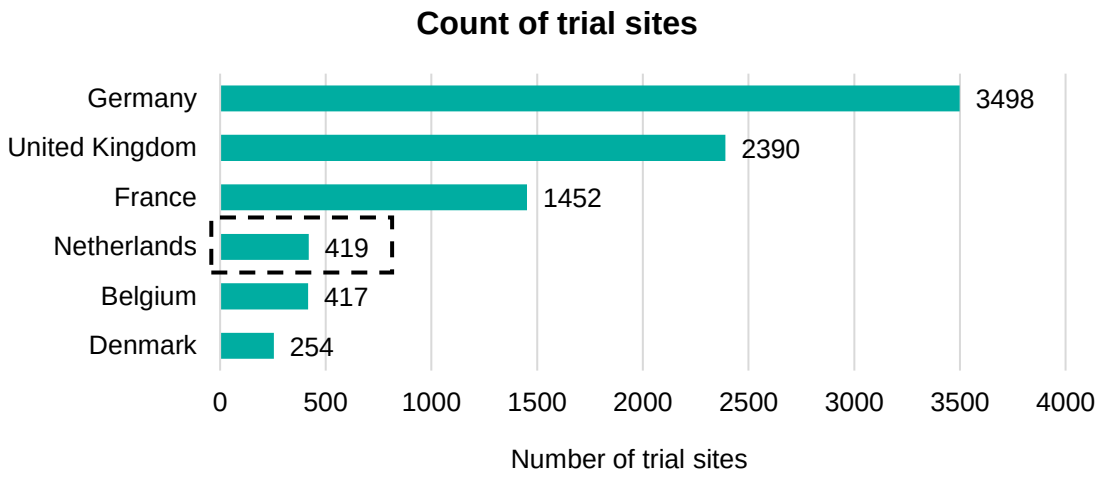
"For paediatric oncology in the Netherlands, eight academic hospitals have merged into one huge centre. That's the Princess Maxima Medical Centre. It is the biggest centre in Western Europe"

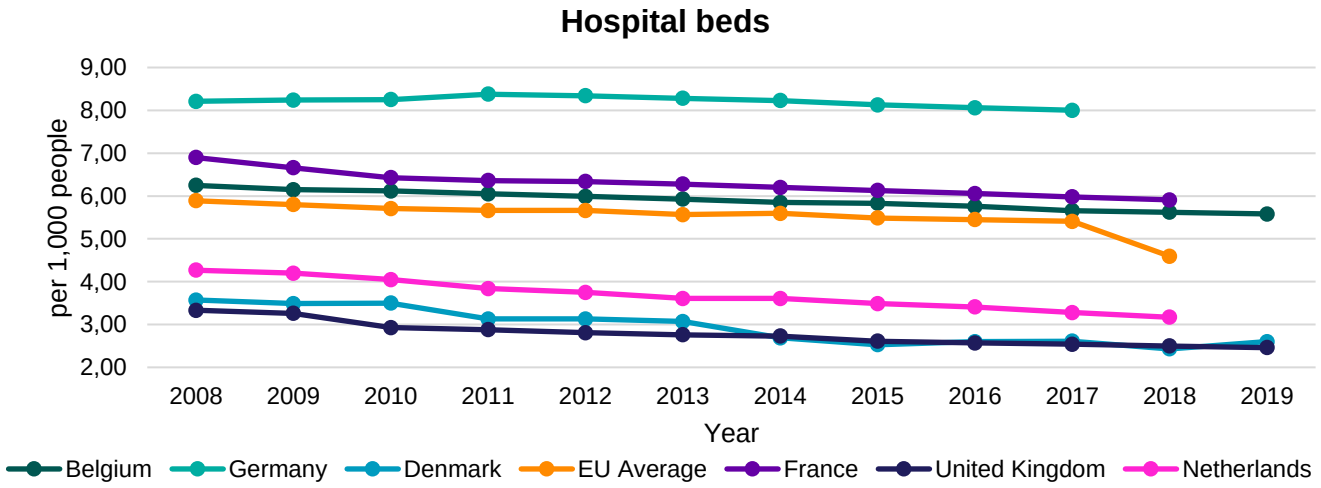


Key figures supporting SWOT analysis – infrastructure for clinical research









Abbreviations

Abbreviation	Meaning
ALS	Amyotrophic Lateral Sclerosis
ATMP	Advanced Therapy Medicinal Products
CCMO	Central Committee on Research Involving Human Subjects
CNS	Central Nervous System
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CTA	Clinical Trial Agreement
CTC	Clinical Trial Coordinator
DCT	Decentralised Clinical Trial
EHR	Electronic Health Record
eISF	Electronic Investigator Site File
EUCTR	EU Clinical Trial Regulation
VRN	Vascular Research Network
WCN	Vereniging Werkgroep Cardiologische centra Nederland

CITELINE