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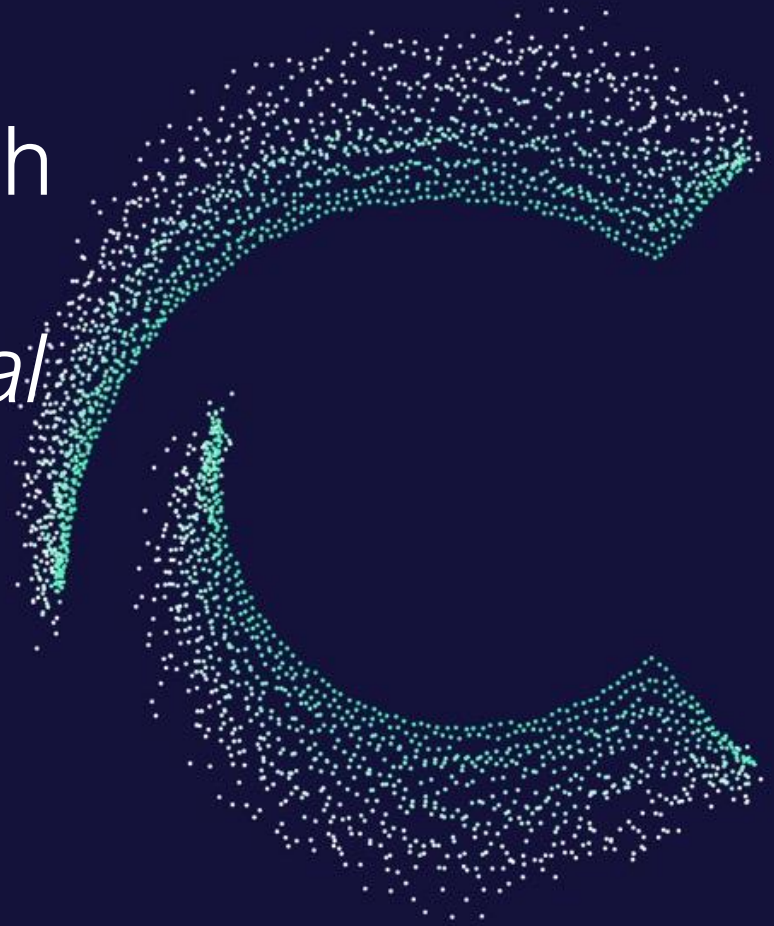
EU Benchmark Clinical Research

The Netherlands as a clinical trial location in Europe



Created by Citeline Custom Intelligence

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Table of Contents

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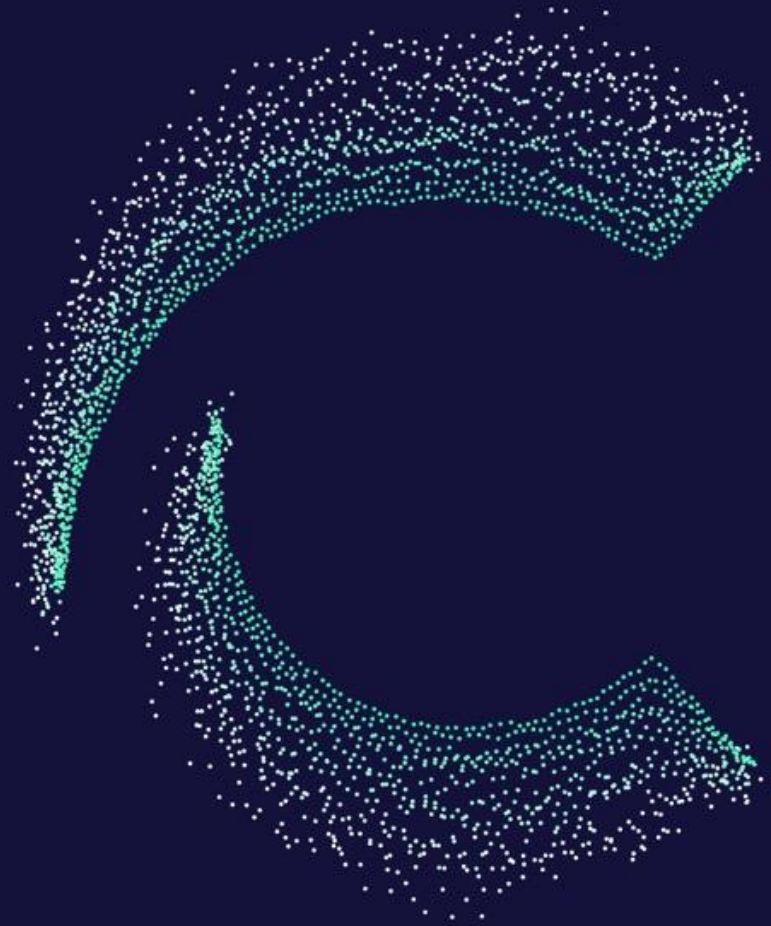
1. Methodology



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Project phases

Phase 1 Project kick off meeting	Phase 2 Secondary research	Phase 3 Country profiling	Phase 4 Primary research	Phase 5 Final analysis/report
▪ Client and Citeline will discuss expectations and chart the course of the project ▪ Confirm objectives and methodologies ▪ Gather internal resources and knowledge in order to avoid duplication and speed up the data collection process ▪ Agree on timelines and communication plans	▪ Secondary research using Citeline internal and external datasets, creation of in-depth comparative clinical trials landscape for the Netherlands to include internal (i.e., provincial) and external (i.e., European) benchmarks	▪ This phase of the project would focus on country-level profiling. ▪ Citeline has assumed there will be N=6 countries from EU4, UK, the Netherlands, Belgium and Denmark	▪ Qualitative interviews (N=6) with key stakeholders who have in-depth knowledge of the Dutch clinical trials ecosystem and can advise at a strategic and tactical level	▪ Actionable, condensed final report analyzing the results of all secondary and primary research to provide insights
Key outputs: ▪ Knowledge sharing ▪ Agreed path forward ▪ Confirmed timelines/communication plans	**Key outputs:** ▪ Clinical trial site landscape analysis within the Netherlands and across European markets	**Key outputs:** ▪ Country-level profiles and comparative analysis vs. the Netherlands	**Key outputs:** ▪ SWOT analysis based on the landscape analysis and online survey ▪ Key strategic insights to mitigate risks and optimise opportunities	**Key outputs:** ▪ Final report (PPT), including executive summary

Important notes regarding data presentation

Definition of the data set used for this Part 2 analysis

The analysis primarily focuses on trials identified with the following inclusion criteria:

Trial status	Ongoing trial + terminated + completed
Data time period *	5 years Unless specified, trials included in the analysis with a start date from 1 January 2018 - 31 December 2022
Sponsor types	All (including industry only, collaboration between industry and academic, and non-industry)

Comparisons are also made to the **current status** of trials in the **Netherlands**, which is defined as:

Trial status	Ongoing (open, closed, temporarily closed)
Data time period *	Trial start date from 1 January 2013 – 31 December 2022
Sponsor types	All (including industry only, collaboration between industry and academic, and non-industry)

6 EU comparator countries:

Please note

Phases: Dual phase trials are rounded up to the next highest phase (e.g., a Phase 1/2 trial is counted as a Phase 2 trial)

Adjusting for population size:

- When comparing the Netherlands to the 6 European comparator countries, in certain cases numbers are adjusted to account for differences in population size (i.e., they are presented as **trials per 10,000 population**)
- The source for the population sizes for each of the 7 countries is the 2021 data from The World Bank

ATMPs: For the purpose of this report we have defined this as cellular and gene therapy products

*There is a time lag in the trial registry data collection. Therefore a small proportion of data in 2022 may not be captured in the database. This effect would be consistent among countries, therefore minimal impact is expected when conducting comparisons between Netherlands and other EU countries.

Trialtrove database coverage scope and search string

Scope

Trialtrove's coverage is focused on drug trials with a primarily prospective time perspective. Trials which do not involve a drug (for example device trials, behavioral studies etc.), or which have a retrospective time perspective (i.e. use observations collected predominantly prior to subject selection and enrollment) are generally not included.

Trialtrove covers a wide range of diseases, including many rare diseases, but not all diseases are in scope for full Trialtrove records. Trials for diseases not currently curated by the analysts but which are listed at ClinicalTrials.gov are added to Trialtrove directly without any curation. These trials will list unassigned as the disease type and therapy area.

Trialtrove search:

The following search string was used to narrow-down to the sub-set of trials of interest, from which analysis was made on specific subsets**:**

TRIAL START DATE (Anticipated and Actual) = 1st Jan 2013 to 31st December 2022
TRIAL REGION = Europe

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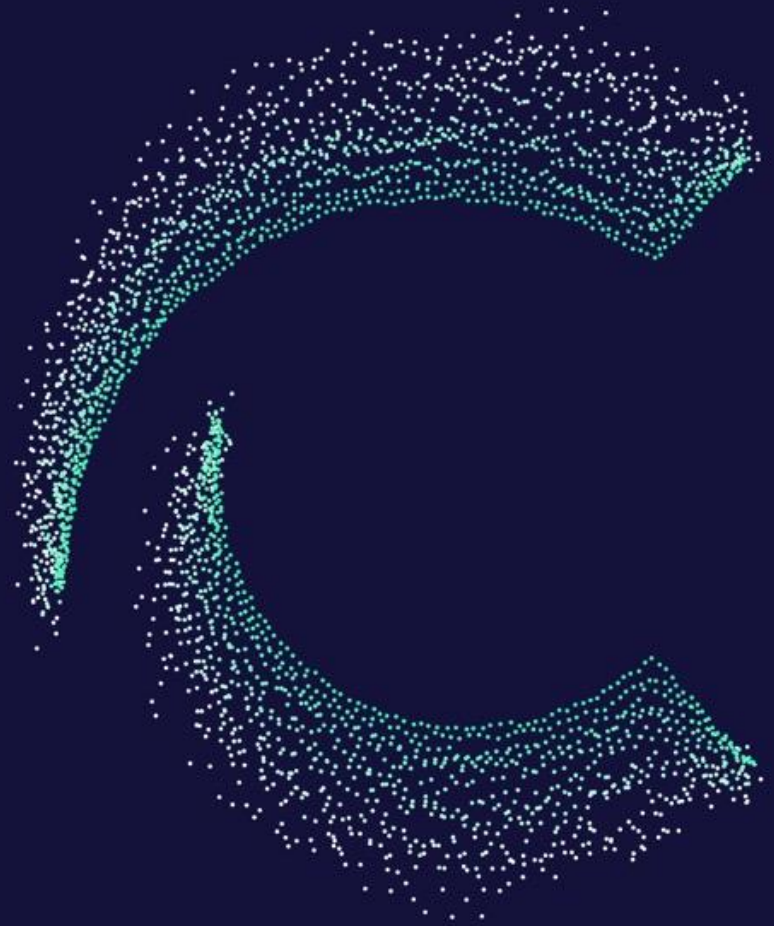
2. EU clinical trial landscape



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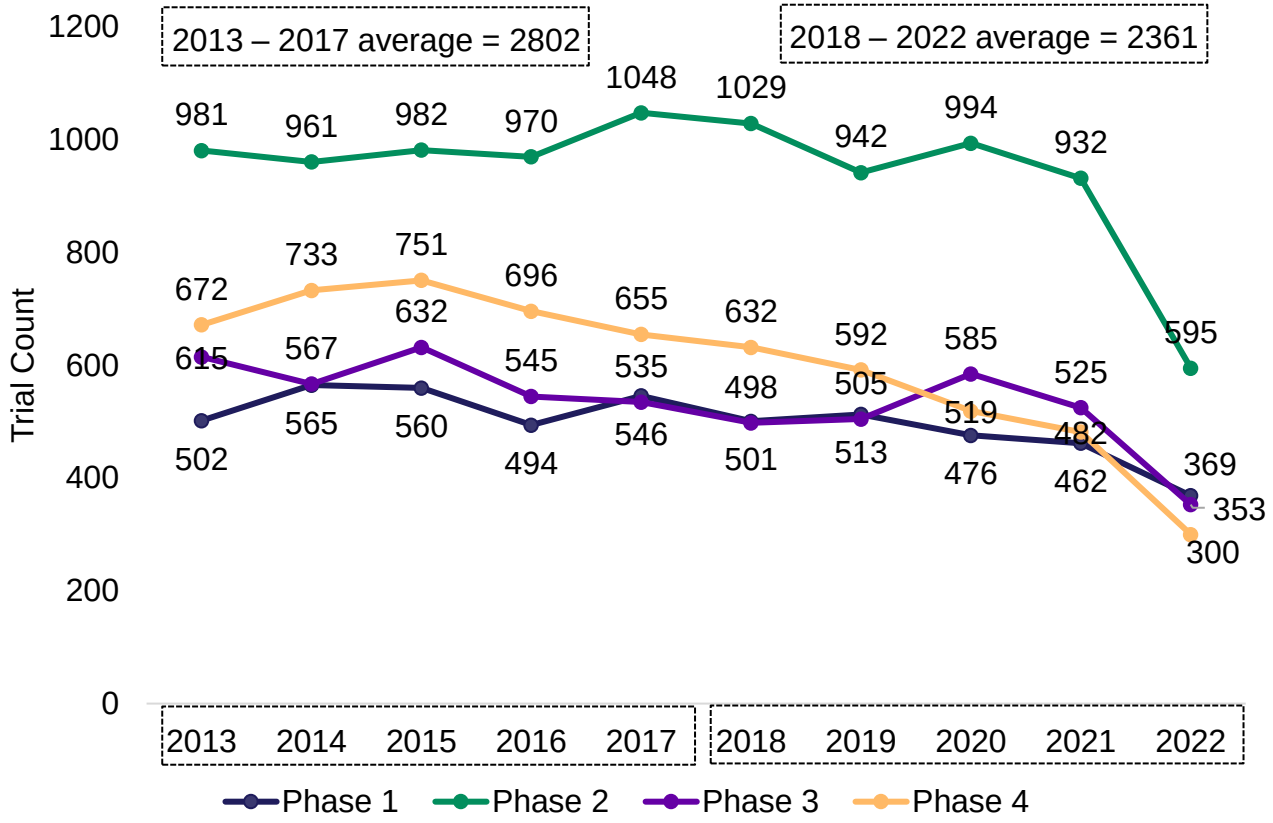
Comparison of trials conducted in 2013-2017 with 2018-2022

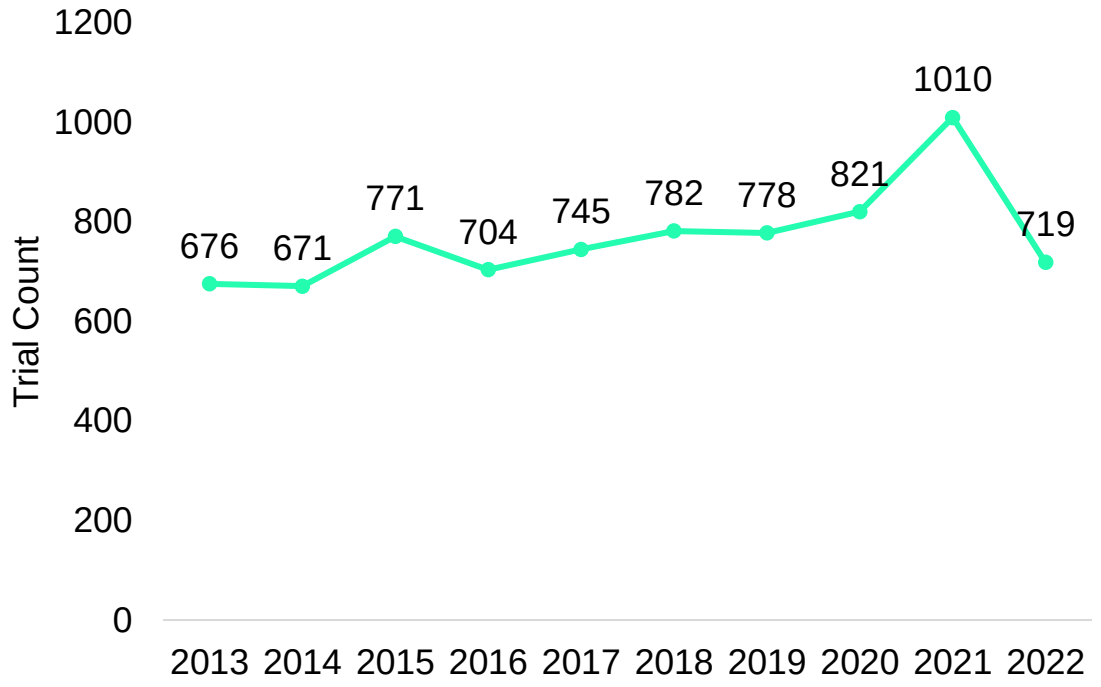
There has been a slight decrease in the number of trials initiated across Europe since the start of the COVID-19 pandemic; average trial initiations dropped by 441 when compared to the previous 5-year period

Count of Trials Initiated across Europe



- Notably, phase 4 trial initiations have seen a sustained decline in every year since 2015

Count of Trials Initiated across North America

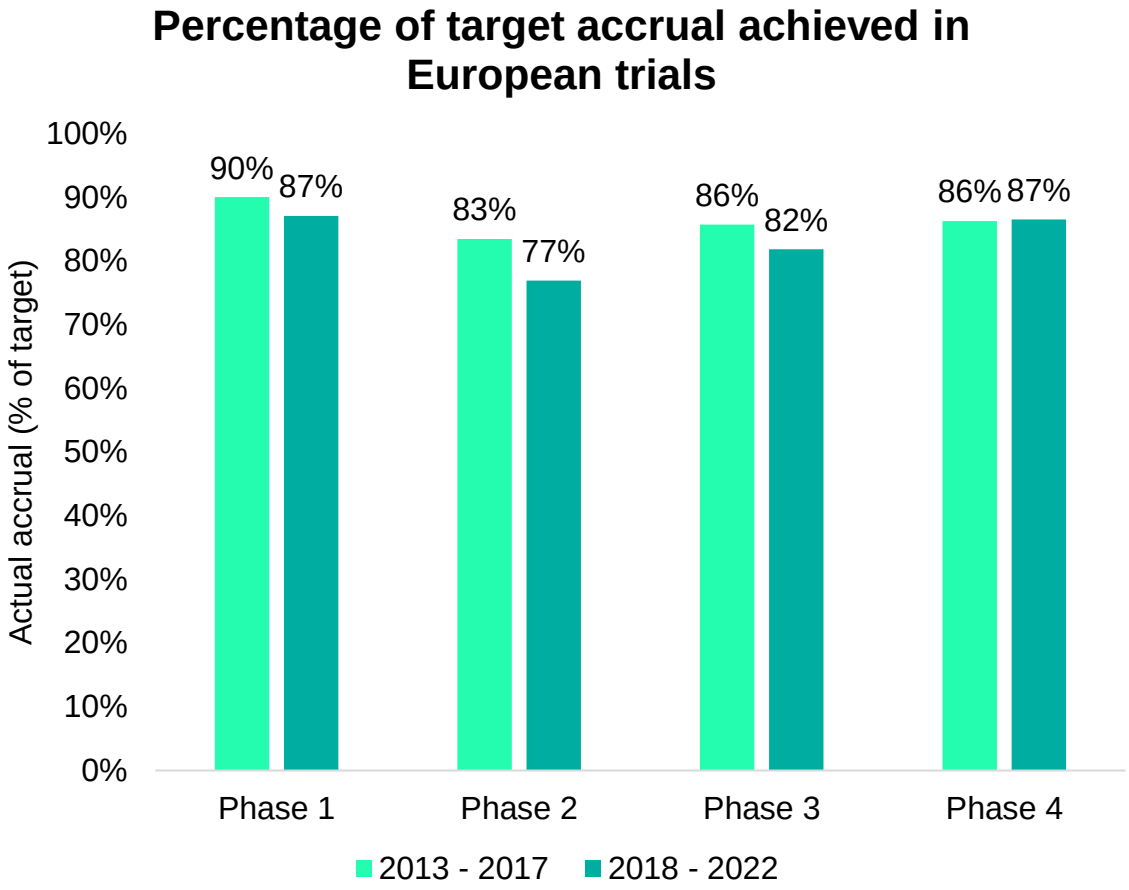


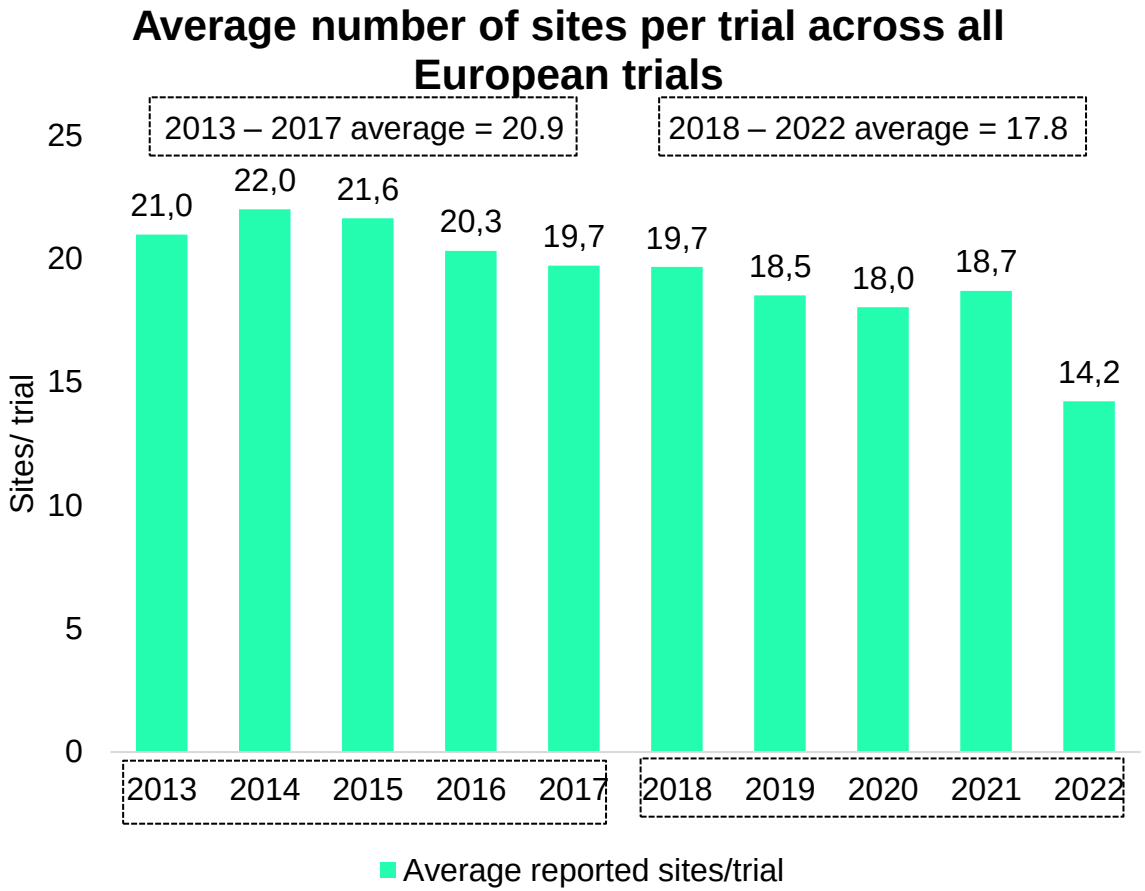
- Counts of open, closed, completed and temporarily closed trials initiated in North America across all phases of development

Source: Citeline| Trialtrove

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

Except for Phase 4, European trials have had a poorer result of achieving their target accrual in recent years; this may be influenced by the fall in the number of sites per trial between 2018 & 2022





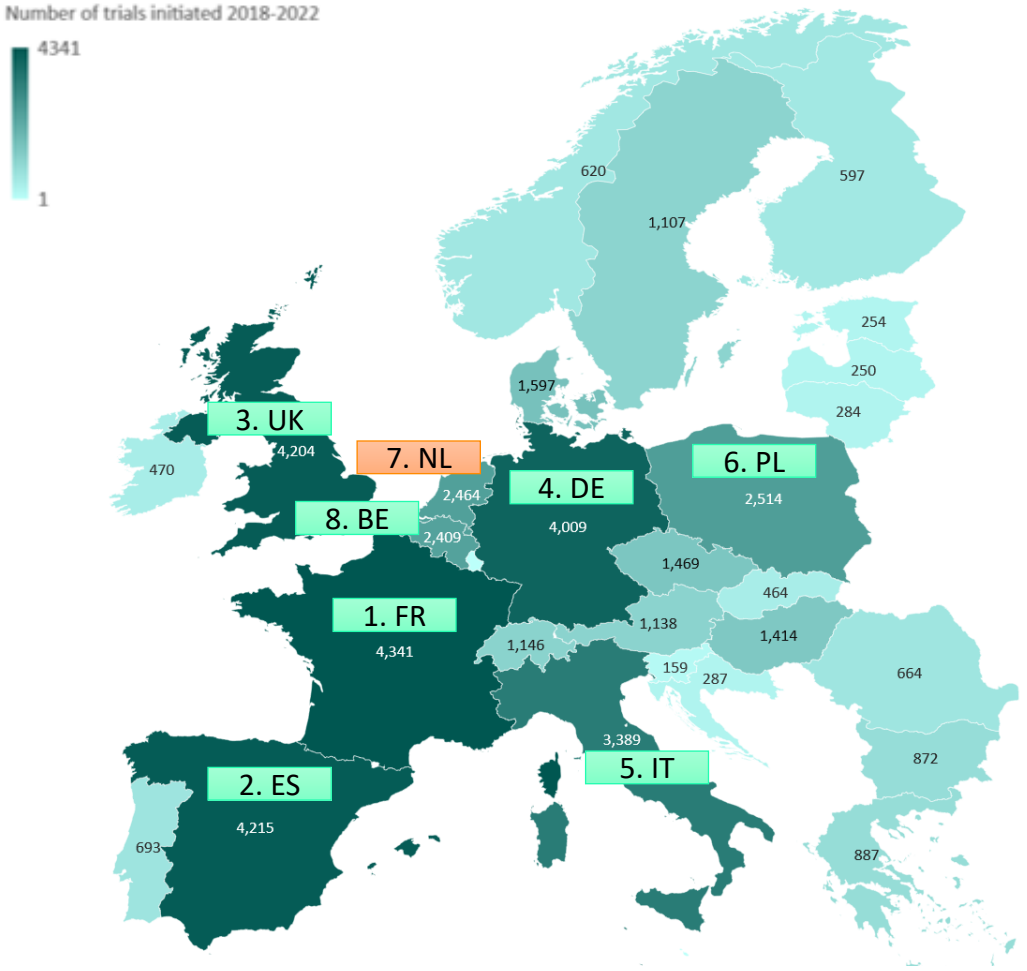
Source: Citeline| Trialtrove

Ranking of the total trials initiated in European countries

The Netherlands ranks 7th among European countries in absolute number of trial initiations between 2018 and 2022

Country	Number of trials initiated 2018-2022	Rank total trials
France	4341	1
Spain	4215	2
United Kingdom	4204	3
Germany	4009	4
Italy	3389	5
Poland	2514	6
Netherlands	2464	7
Belgium	2409	8
Denmark	1597	9
Czech Republic	1469	10
Hungary	1414	11
Switzerland	1146	12
Austria	1138	13
Sweden	1107	14
Greece	887	15
Bulgaria	872	16
Portugal	693	17
Romania	664	18
Norway	620	19
Finland	597	20
Ireland	470	21
Slovakia	464	22
Croatia	287	23
Lithuania	284	24
Estonia	254	25
Latvia	250	26
Slovenia	159	27
Cyprus	16	28
Luxembourg	12	29
Malta	1	30

Trials initiated 2018-2022



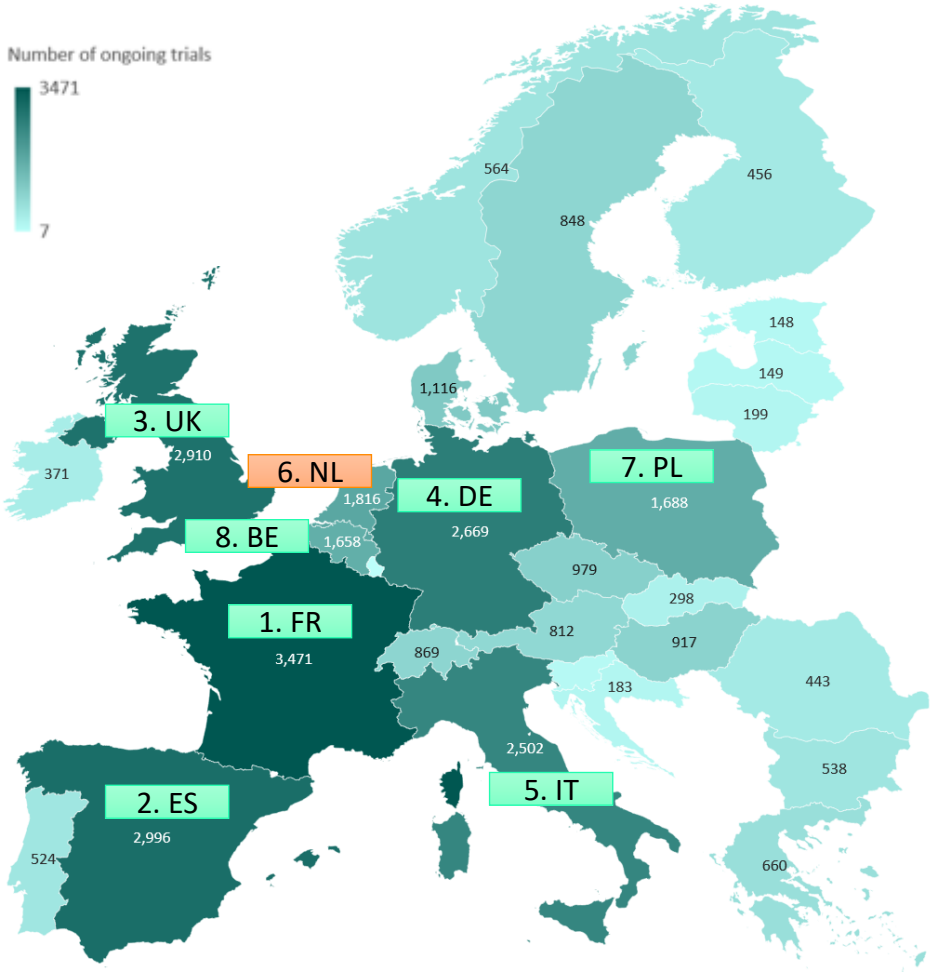
Sources: Citeline| Trialtrove

Ranking of the total on-going trials in European countries

The Netherlands ranks 6th for number of ongoing trials, which is one place higher than for all trial initiations, moving ahead of Poland.

Country	Number of ongoing trials	Rank ongoing trials
France	3471	1
Spain	2996	2
United Kingdom	2910	3
Germany	2669	4
Italy	2502	5
Netherlands	1816	6
Poland	1688	7
Belgium	1658	8
Denmark	1116	9
Czech Republic	979	10
Hungary	917	11
Switzerland	869	12
Sweden	848	13
Austria	812	14
Greece	660	15
Norway	564	16
Bulgaria	538	17
Portugal	524	18
Finland	456	19
Romania	443	20
Ireland	371	21
Slovakia	298	22
Lithuania	199	23
Croatia	183	24
Latvia	149	25
Estonia	148	26
Slovenia	122	27
Cyprus	12	28
Luxembourg	7	29

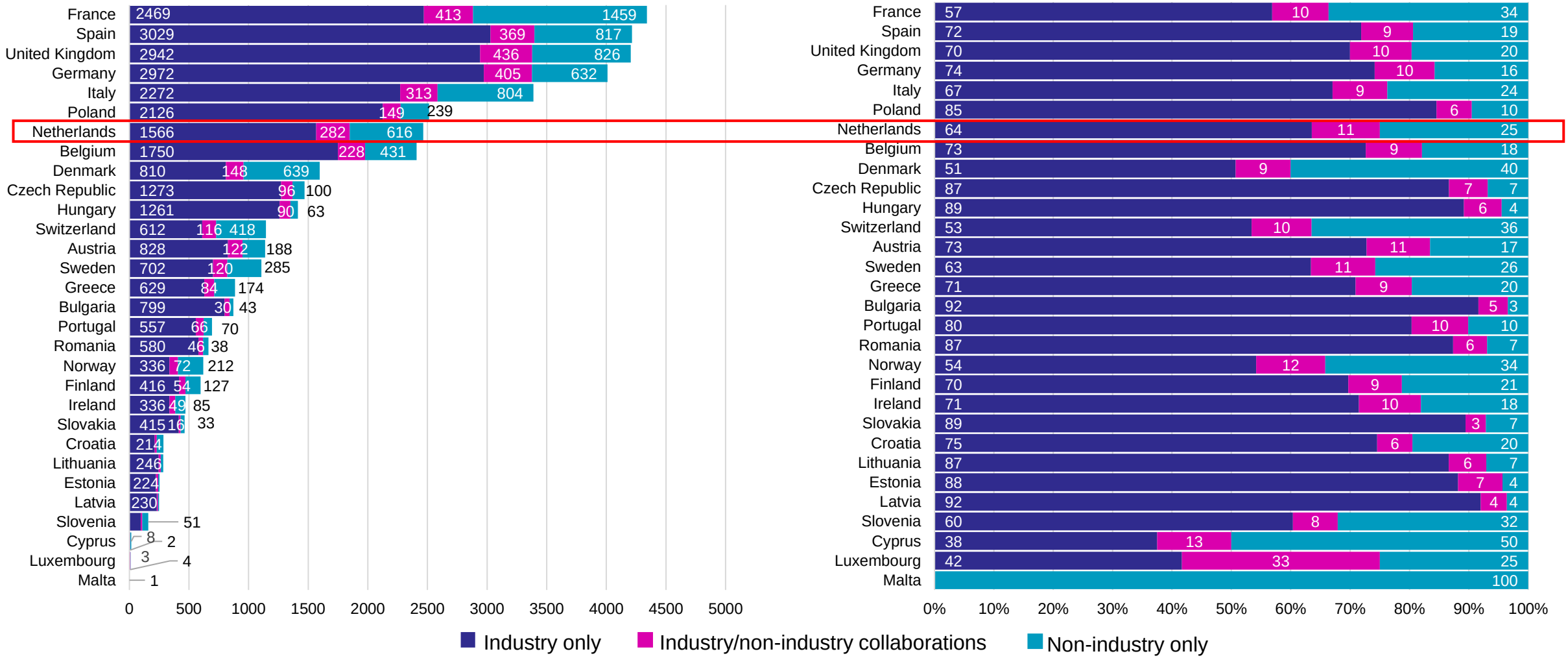
On-going trials



Sources: Citeline| Trialtrove

Industry vs. non-industry proportions in Europe

In the Netherlands, 75% of trials include at least one industry sponsor, which falls below the European median of 81% for trials with industry sponsors

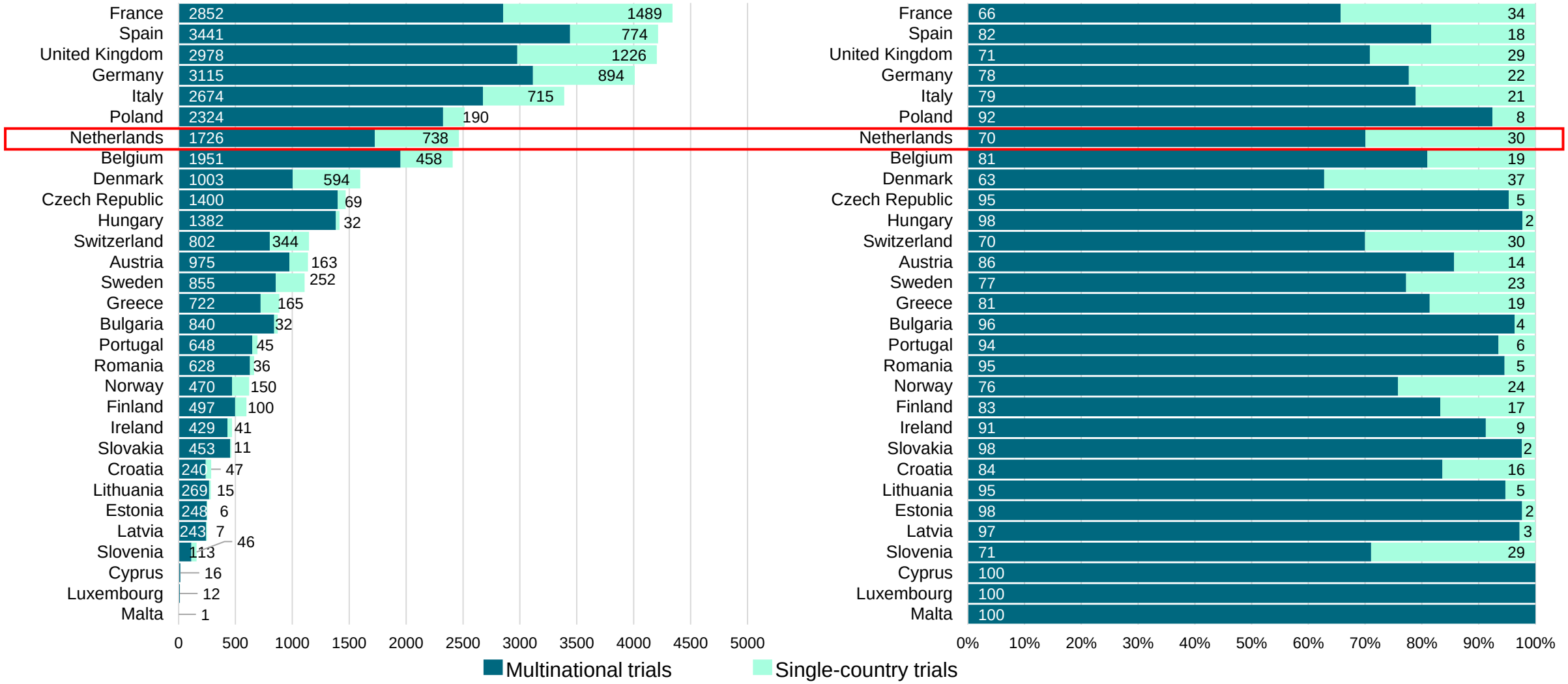


"Industry only" = trials which are only associated with industry sponsors; "Industry/non-industry collaborations" = trials which have at least one industry sponsor and a sponsor of another type (Includes government / cooperative group / miscellaneous / OTC / not for profit collaborations); "Non-industry only" = trials which are associated with zero industry sponsor (Includes academic / government / cooperative group / miscellaneous / OTC / not for profit)

Sources: Citeline| Trialtrove

Analysis of multinational Vs single country trials for all of Europe

30% of trials run in the Netherlands are single-country trials; only France, Switzerland and Denmark have a higher percentage of single country trials



Sources: Citeline| Trialtrove

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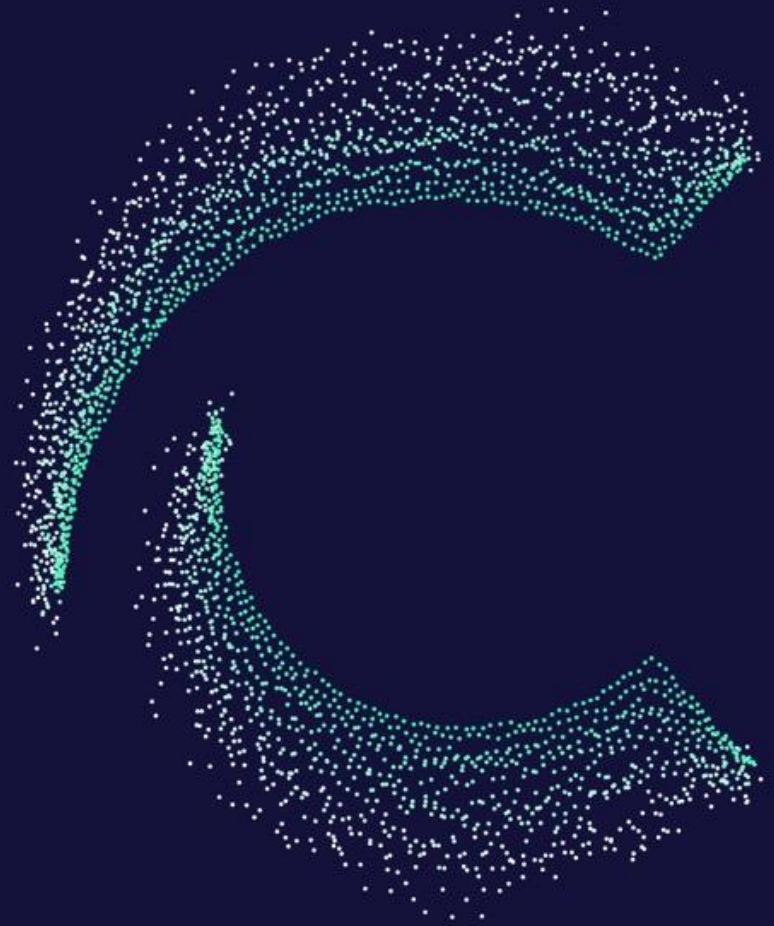
3. Netherlands clinical trial landscape



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Overall attractiveness as clinical trial locations

From key player interviews (n=6) the Netherlands ranked 4th overall for clinical trial attractiveness, influenced by lengthy contracting processes and therapeutic area challenges; however, it is highly regarded for early-phase studies

Rank	Key player 1	Key player 2	Key player 3	Key player 4	Key player 6
1	Germany	Germany	France	France	Belgium
2	UK	UK	Germany	UK	France
3	**Netherlands**	Belgium	UK	Belgium	Germany
4	Denmark	France	4th= **Netherlands**	**Netherlands**	**Netherlands**
5	France	**Netherlands**	4th= Belgium	Denmark	Denmark
6	Belgium	Denmark	4th= Denmark	Germany	UK

Rank	Average
=1	Germany
=1	France
2	UK
3	Belgium
4	**Netherlands**
5	Denmark

Reasons for Netherlands ranking

1. Lengthy contracting and recruitment difficulties
2. Different strengths in therapeutic areas
3. Challenges with vaccine clinical trials
4. Translations to Dutch/Flemish is an additional complexity

"They're quite picky on which trials they want, and the contracting procedure can be quite lengthy." – ***Key player 4***

Early- vs late-phase studies in the Netherlands

- 3 out of 5 key players expressed that the Netherlands is **highly regarded for phase I studies**
- Key player 3 highlighted the Netherlands' Cancer Institute's strength in phase I oncology, ranking it amongst the top five centres globally
- For late-phase studies, key players maintained the same ranking or considered it lower in comparison

Reasons for top rankings

1. Shorter startup timelines
2. Efficient recruitment
3. Large population fuels more trials
4. Good infrastructure
5. High quality research sites

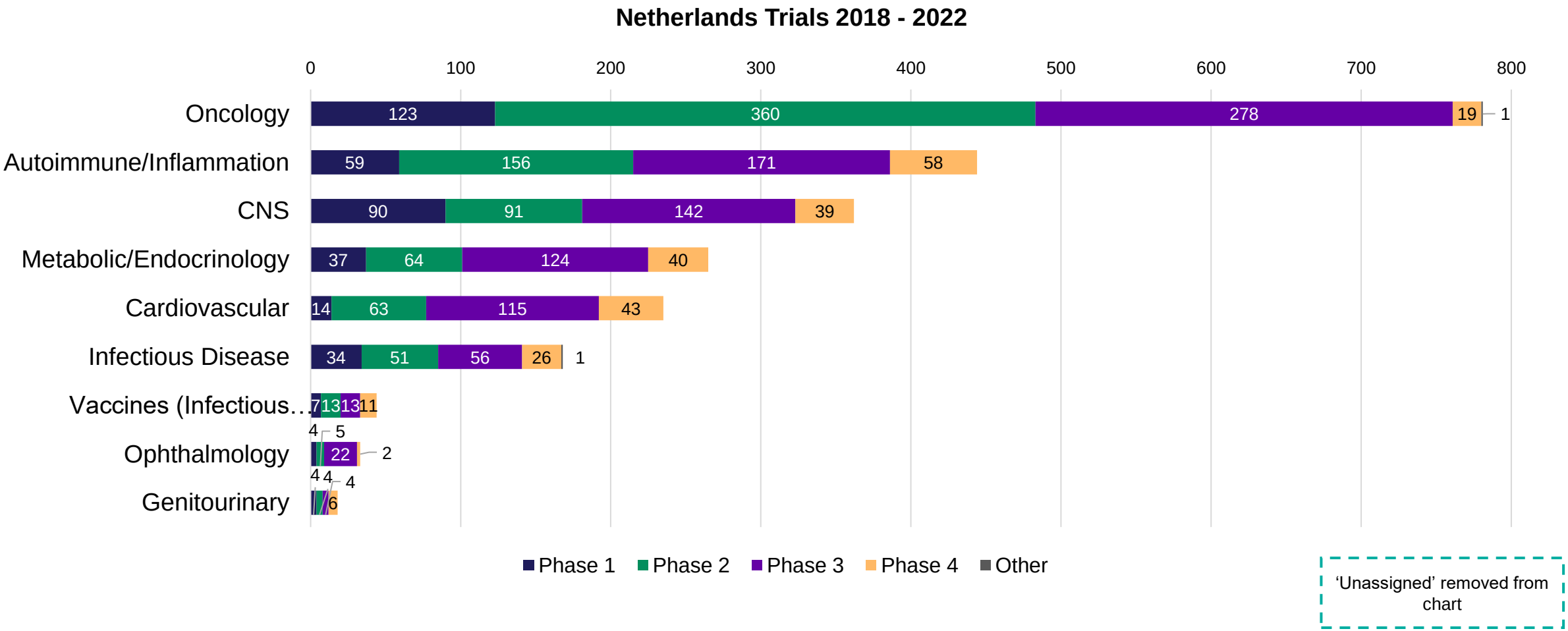
"Because of the fast startup timelines and good recruitment in general, and good quality." – ***Key player 6***

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

KP 5 did not have insight

Netherlands TAs split by phase (2018-2022)

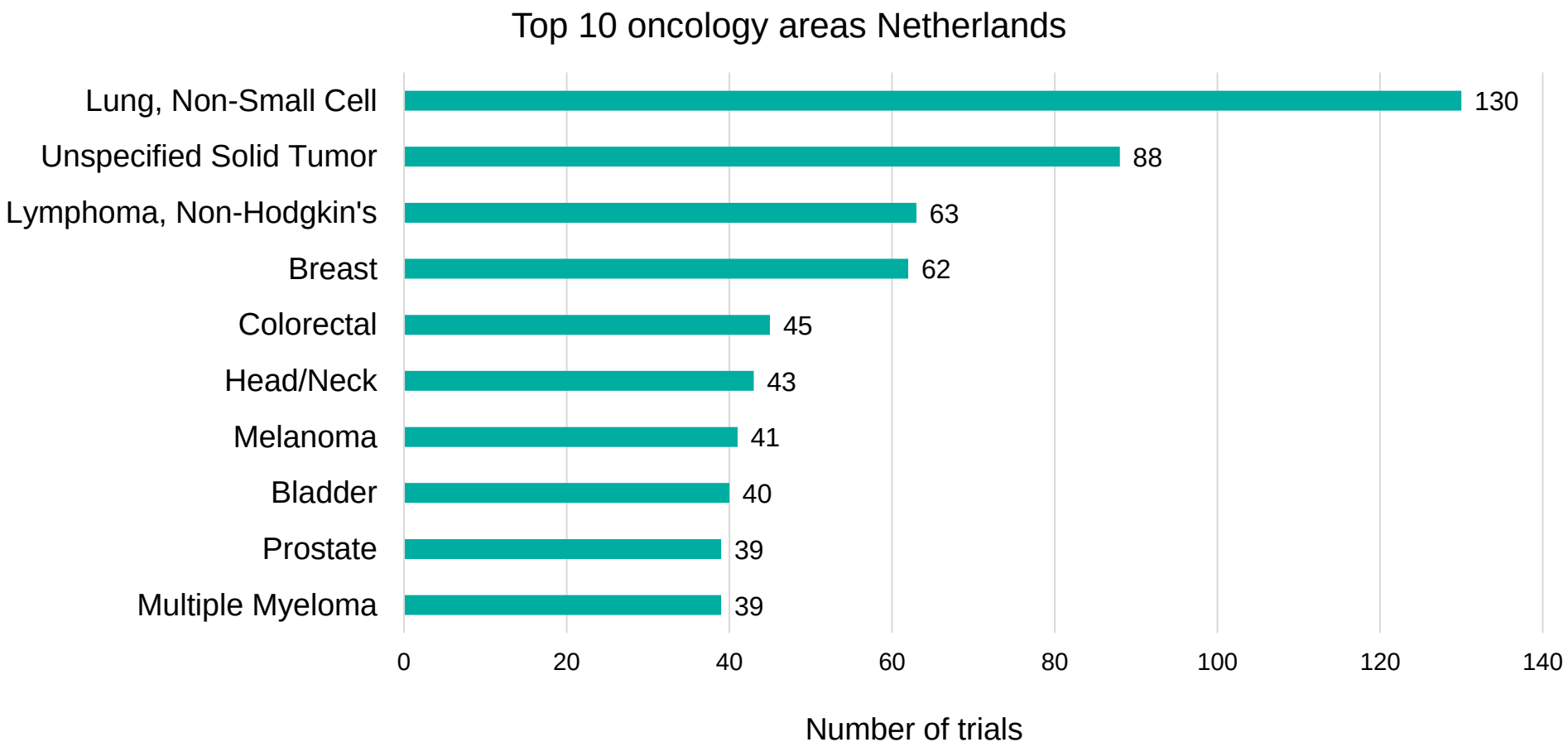
The most common therapeutic area for clinical trial activity in the Netherlands over the past 5 years is Oncology, specifically Phase 2 and 3 activity



Sources: Citeline| Trialtrove

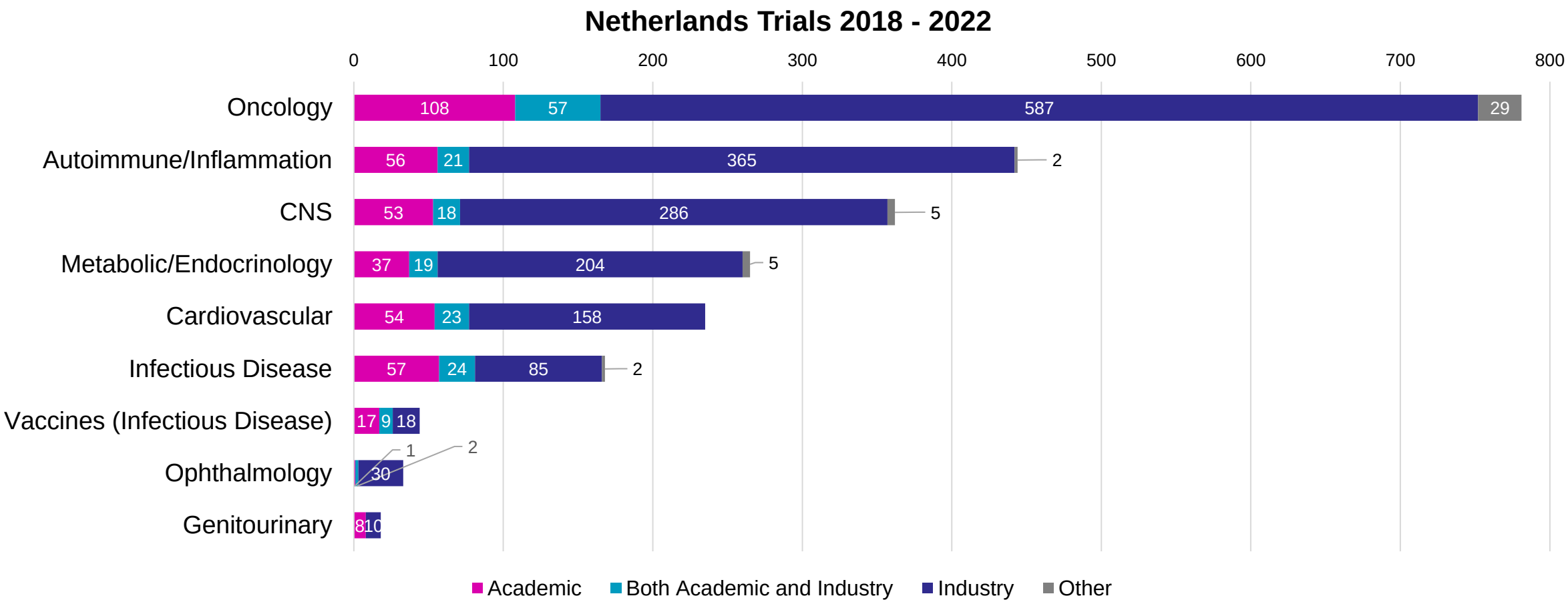
Deep dive into Oncology: multi-country trials by disease

The top 10 oncology diseases in Netherland's based trials largely align with the comparator countries, however, Prostate cancer trials rank the highest in Netherlands at joint 9th place



Netherlands, the number of initiated trials in selected TAs split by sponsor type

Industry sponsorship represents the vast majority for all assigned TAs from 2018-2022

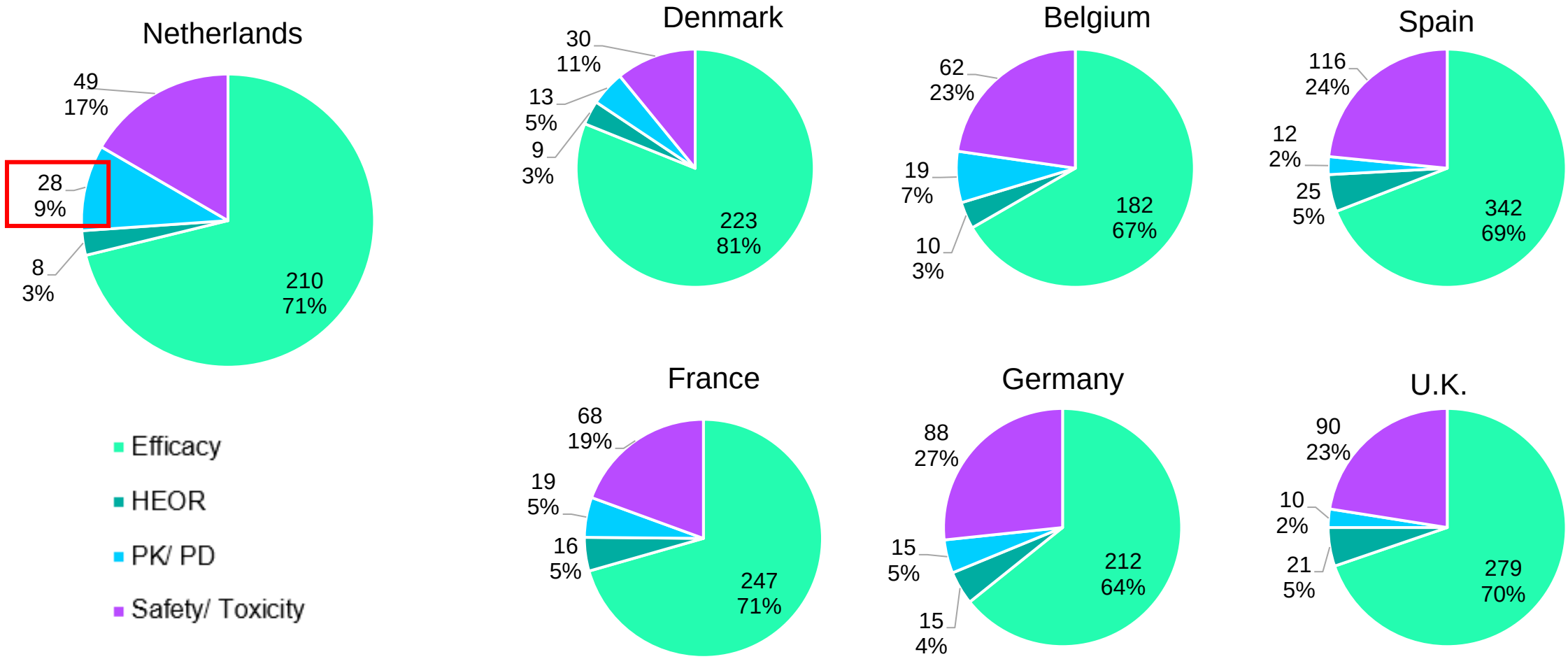


1. 'Unassigned' removed from chart
2. *Includes government / cooperative group / miscellaneous / OTC / not for profit collaborations

Sources: Citeline| Trialtrove; N.B: industry = any trial with an industry sponsor, but not academic; academic = any trial with an academic sponsor but not industry; both industry and academic = any trial with both an industry and academic sponsor; other = any trial that has neither an industry nor academic sponsor

Phase 4 deep-dive: multi-country trials by goals

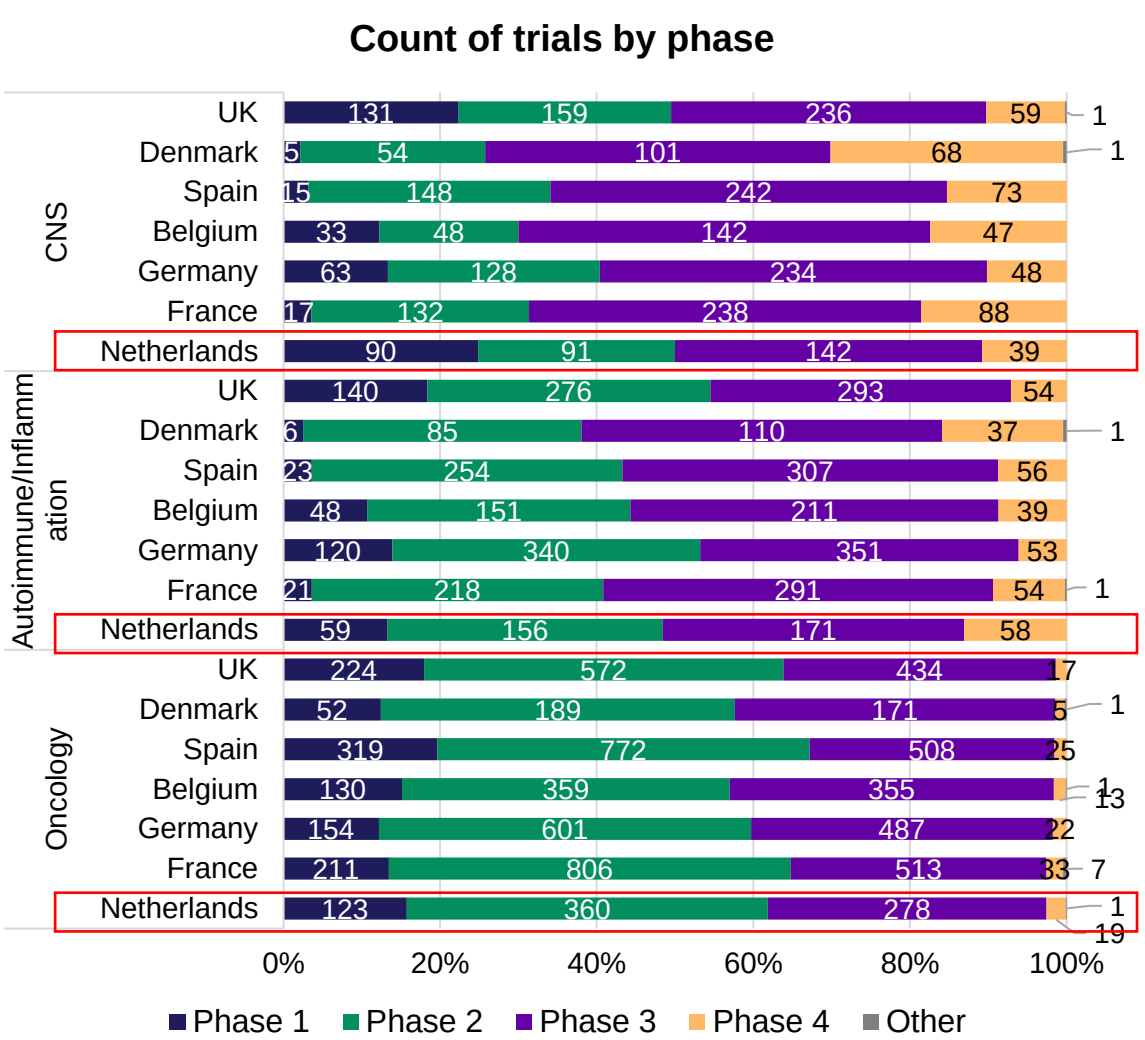
Out of the comparator countries, the Netherlands has the greatest proportion of phase 4 trials assessing pharmacokinetics/ pharmacodynamics

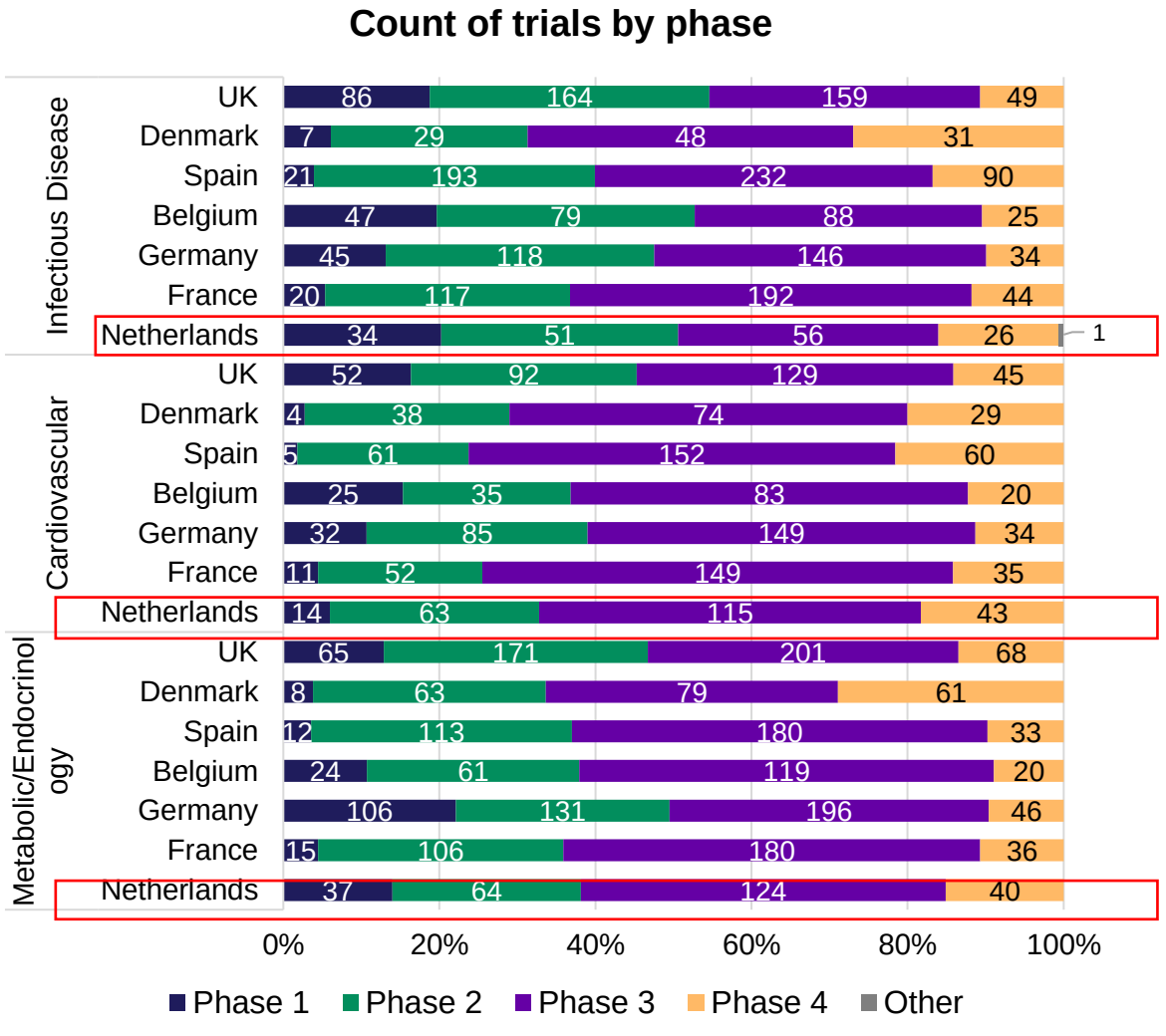


Note: Trials without a tagged goal have been removed from charts

Proportion of trials in each TA by phase (part 1)

While Phase 2 and 3 trials dominate the landscape, relative to other countries, The Netherlands has some of the highest proportions of early stage (Phase 1) trial activity in the past 5 years



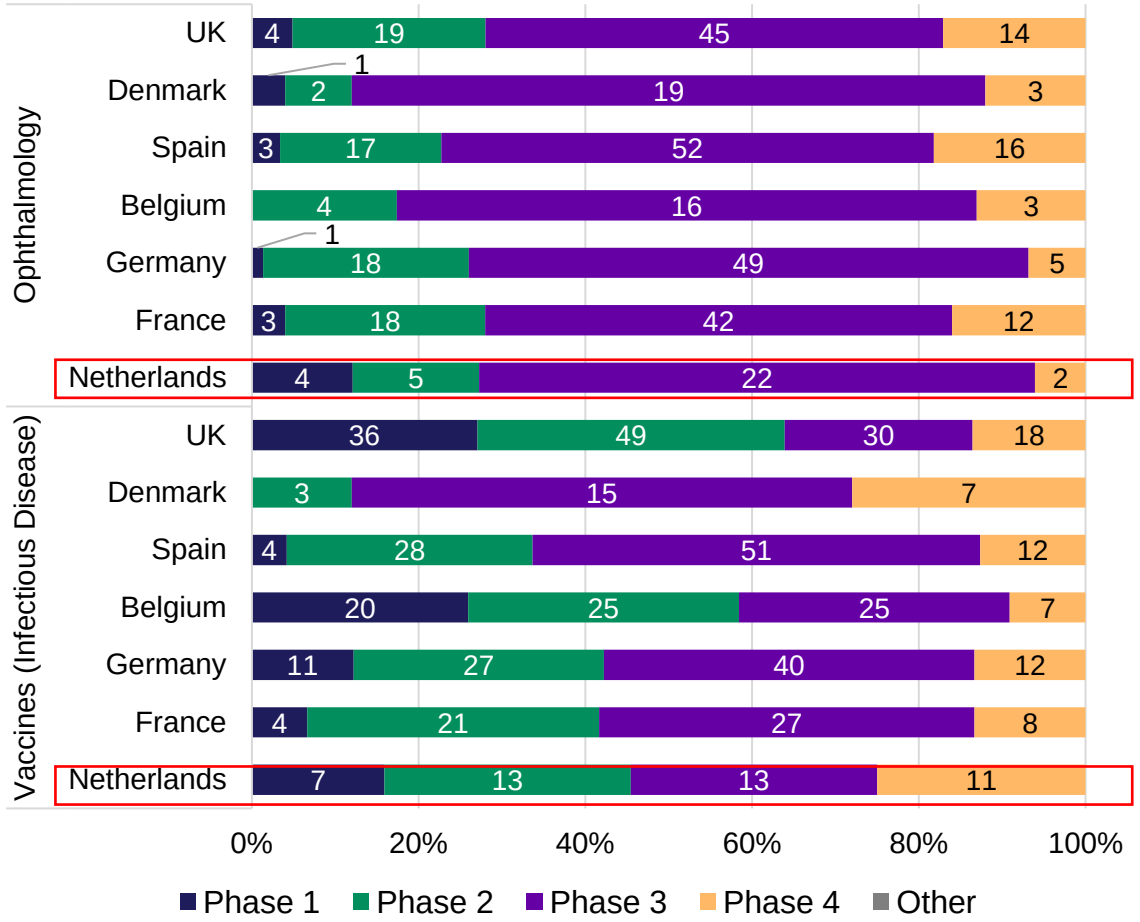


Sources: Citeline| Trialtrove; **N.B:** Data labels are raw values

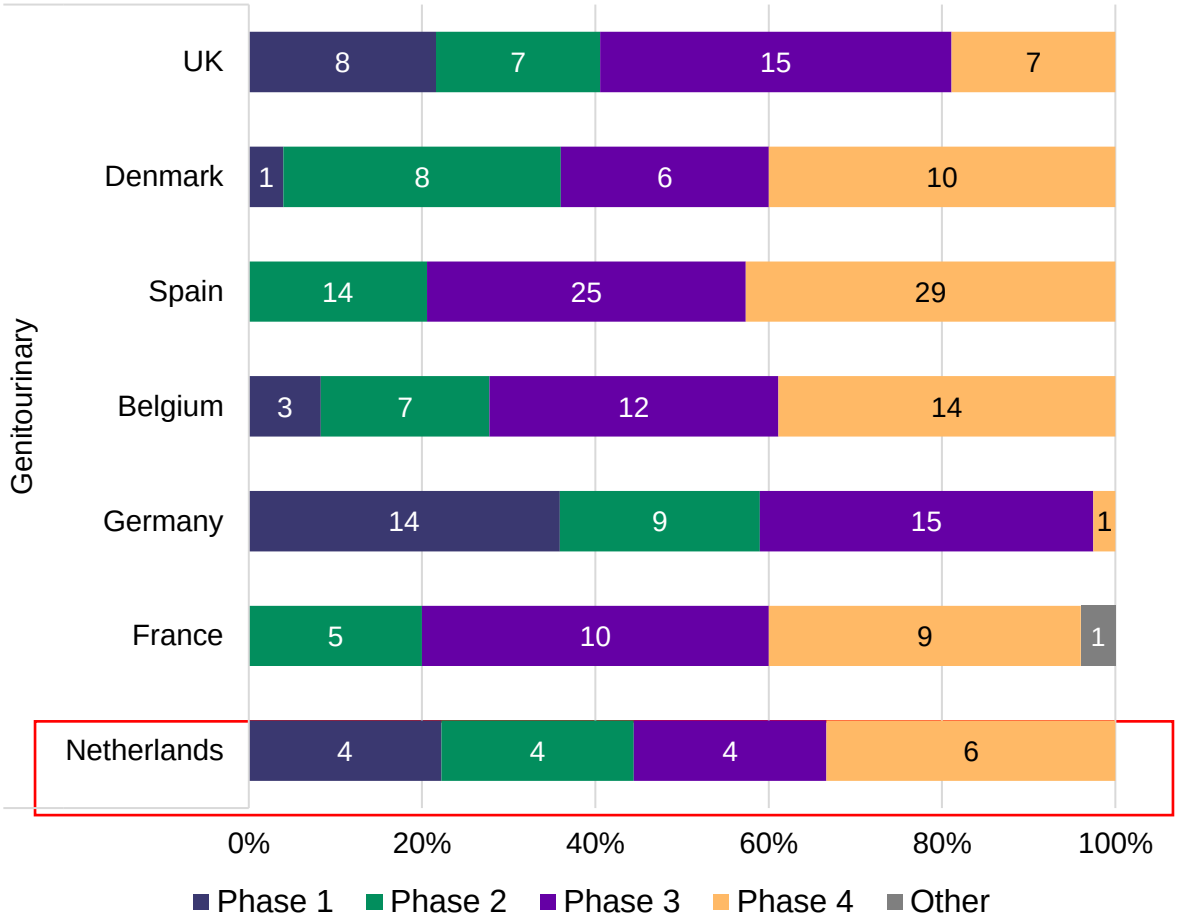
Proportion of trials in each TA by phase (part 2)

While Phase 2 and 3 trials dominate the landscape, relative to other countries, The Netherlands has some of the highest proportions of early stage (Phase 1) trial activity in the past 5 years

Count of trials by phase



Count of trials by phase

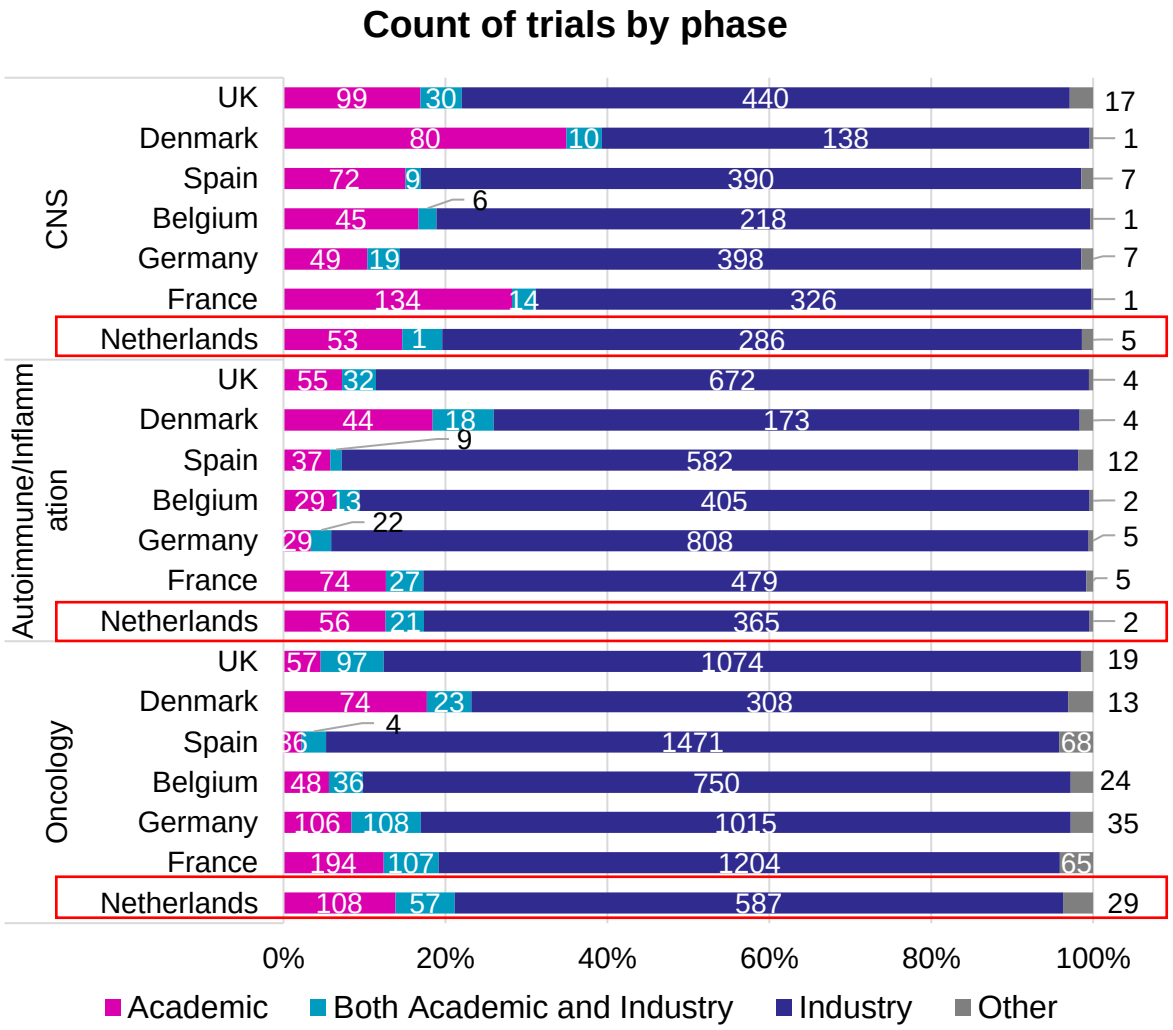


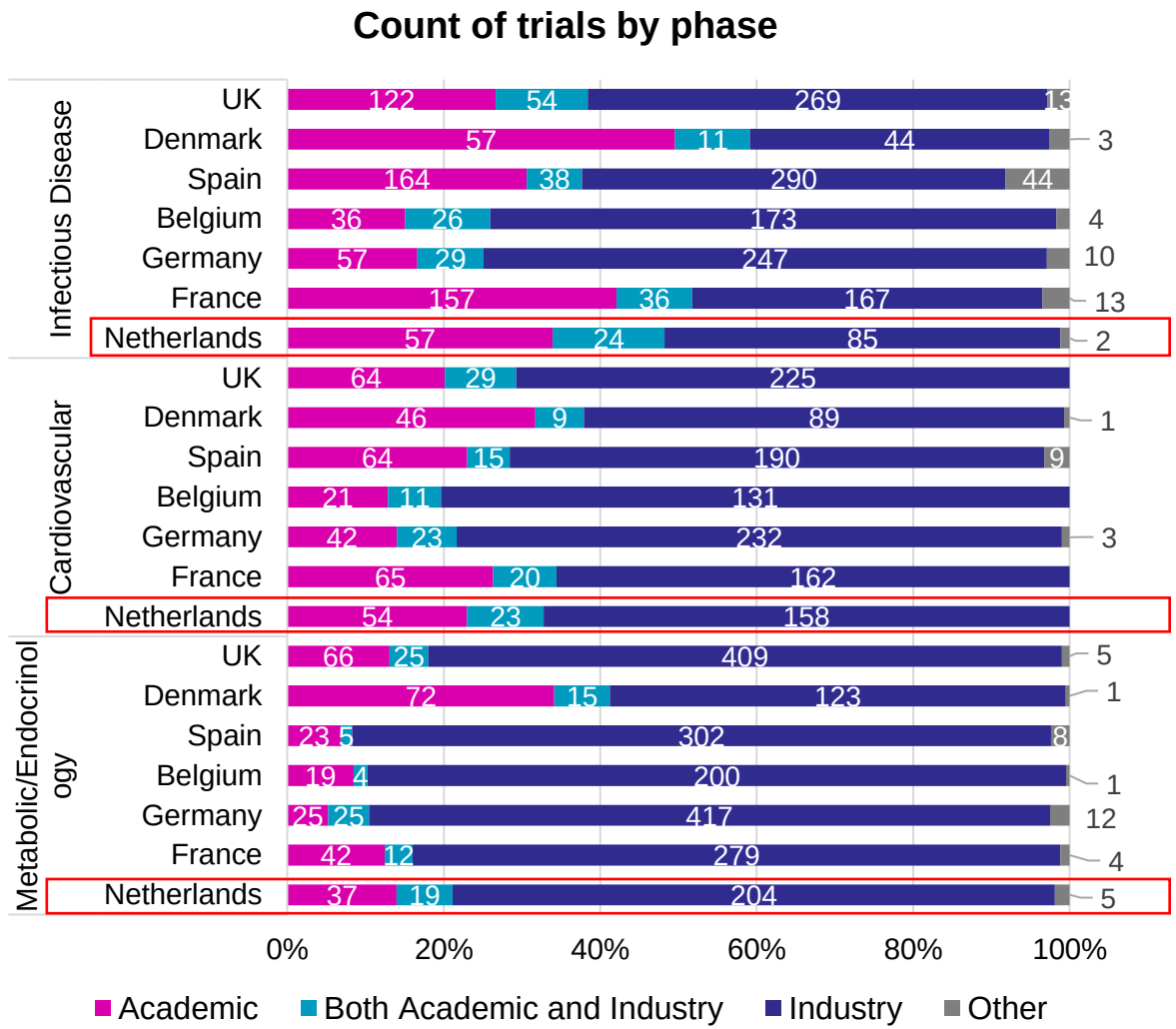
Sources: Citeline| Trialtrove N.B: Data labels are raw values

'Unassigned' removed from charts

Proportion of trials in each TA by sponsor type (1/2)

Relative to the 6 comparator countries, The Netherlands has some of the greatest proportions of academic sponsorship on trials, and in the case of vaccine (infectious diseases) trials, the greatest





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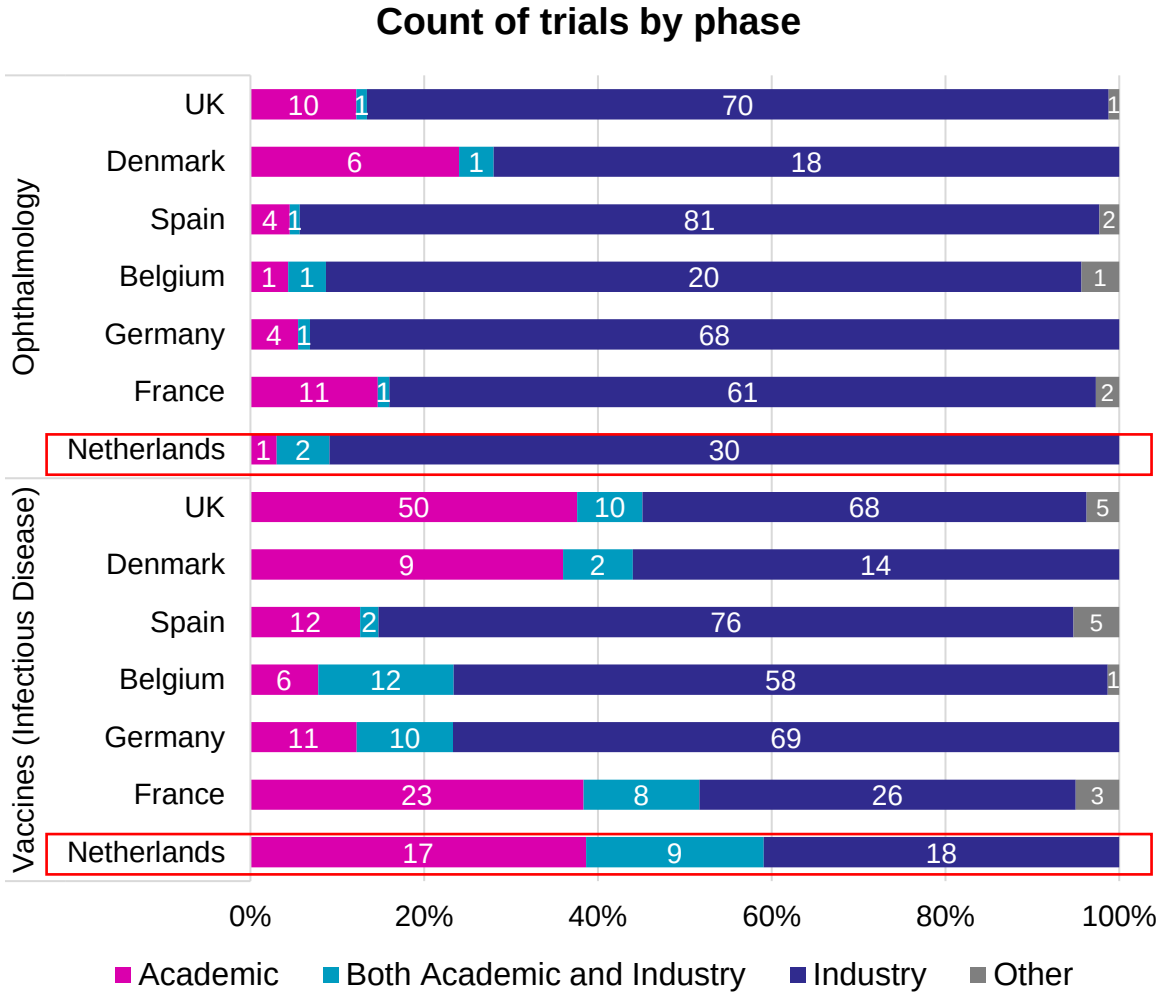
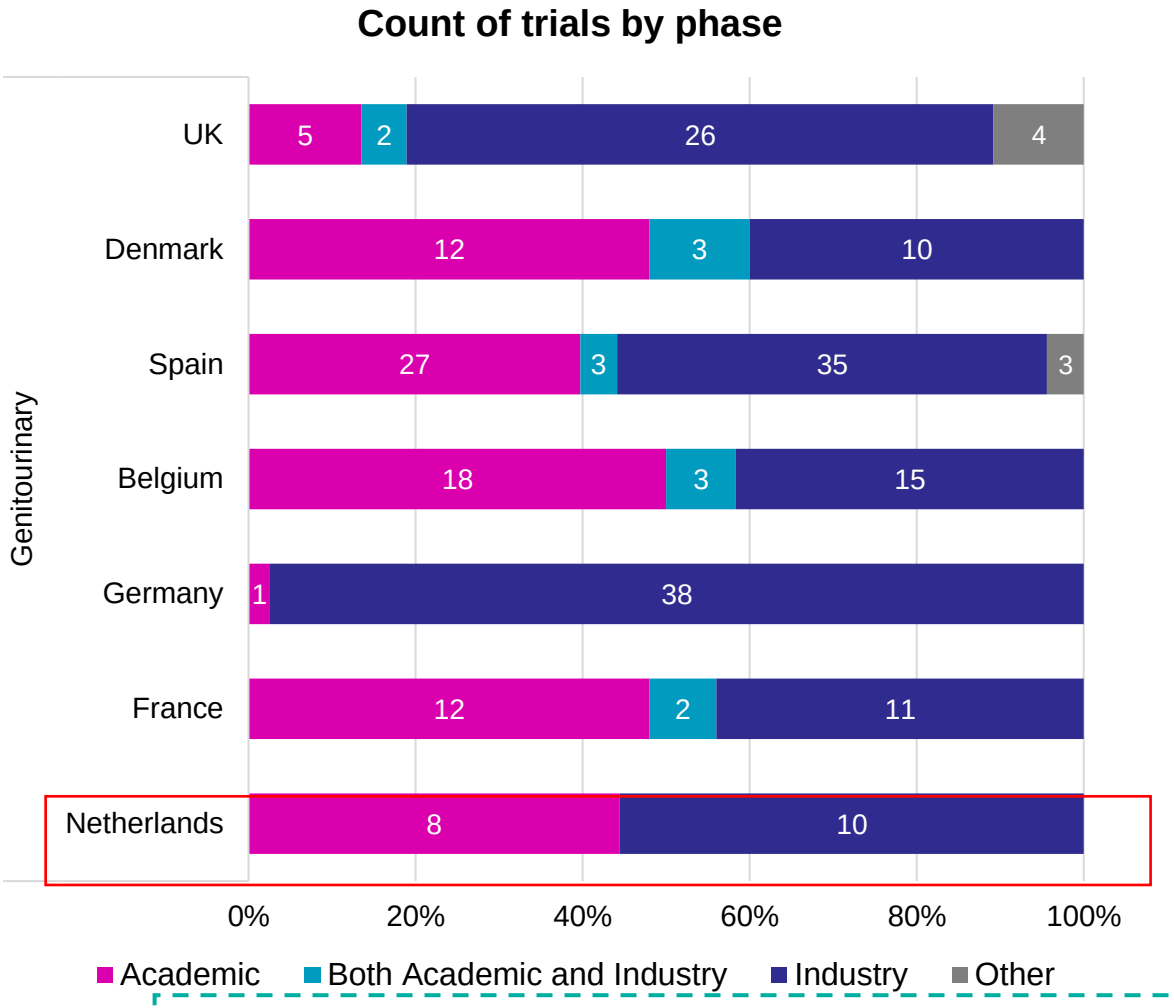
Proportion of trials in each TA by sponsor type (2/2)

Relative to the 6 comparator countries, The Netherlands has some of the greatest proportions of academic sponsorship on trials, and in the case of vaccine (infectious diseases) trials, the greatest





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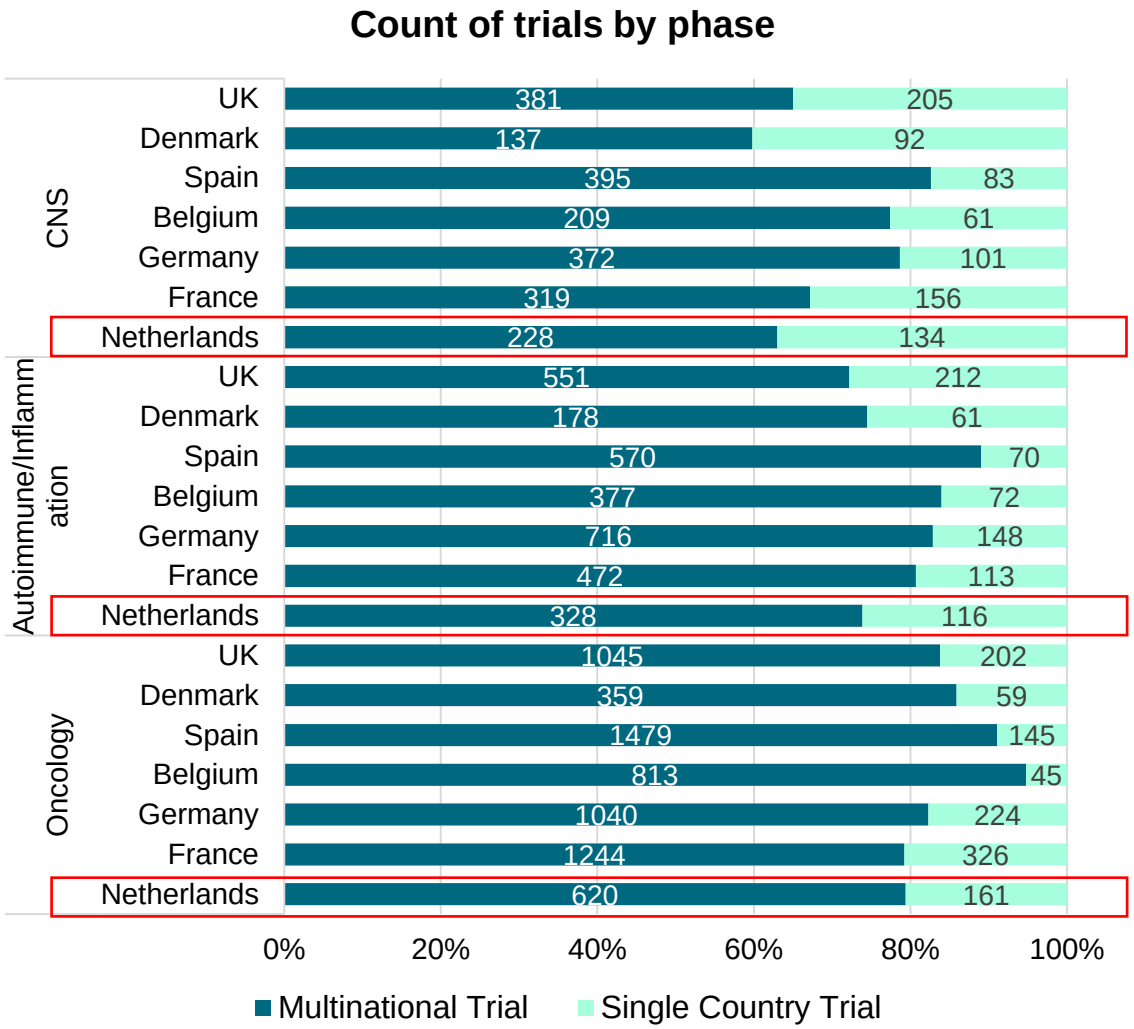
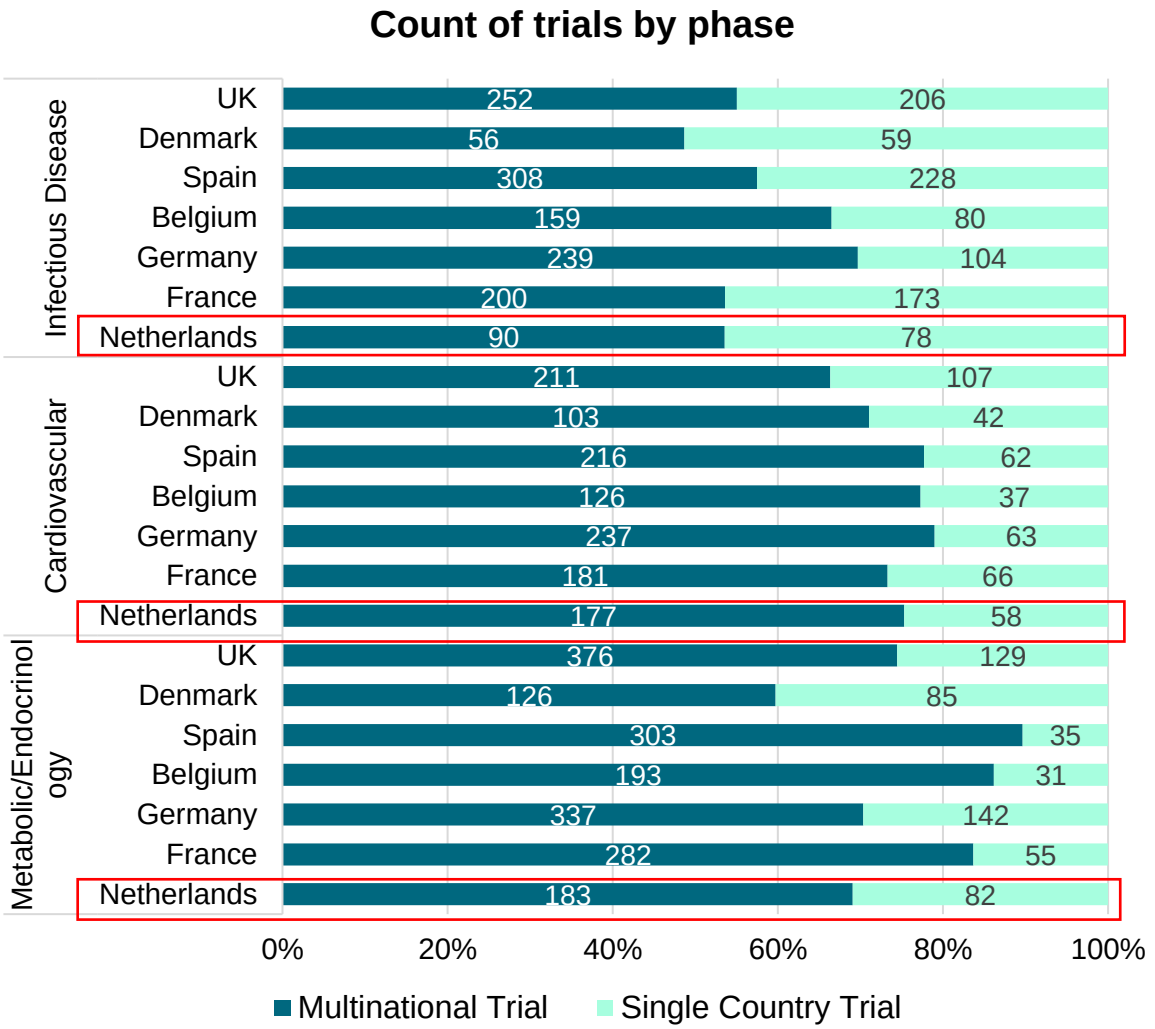
Proportion of trials in each TA by single-country vs multinational (1/2)

Relative to other therapeutic areas, genitourinary, infectious disease, and vaccine (infectious diseases) trials tend to have a greater proportion which are located in a single-country

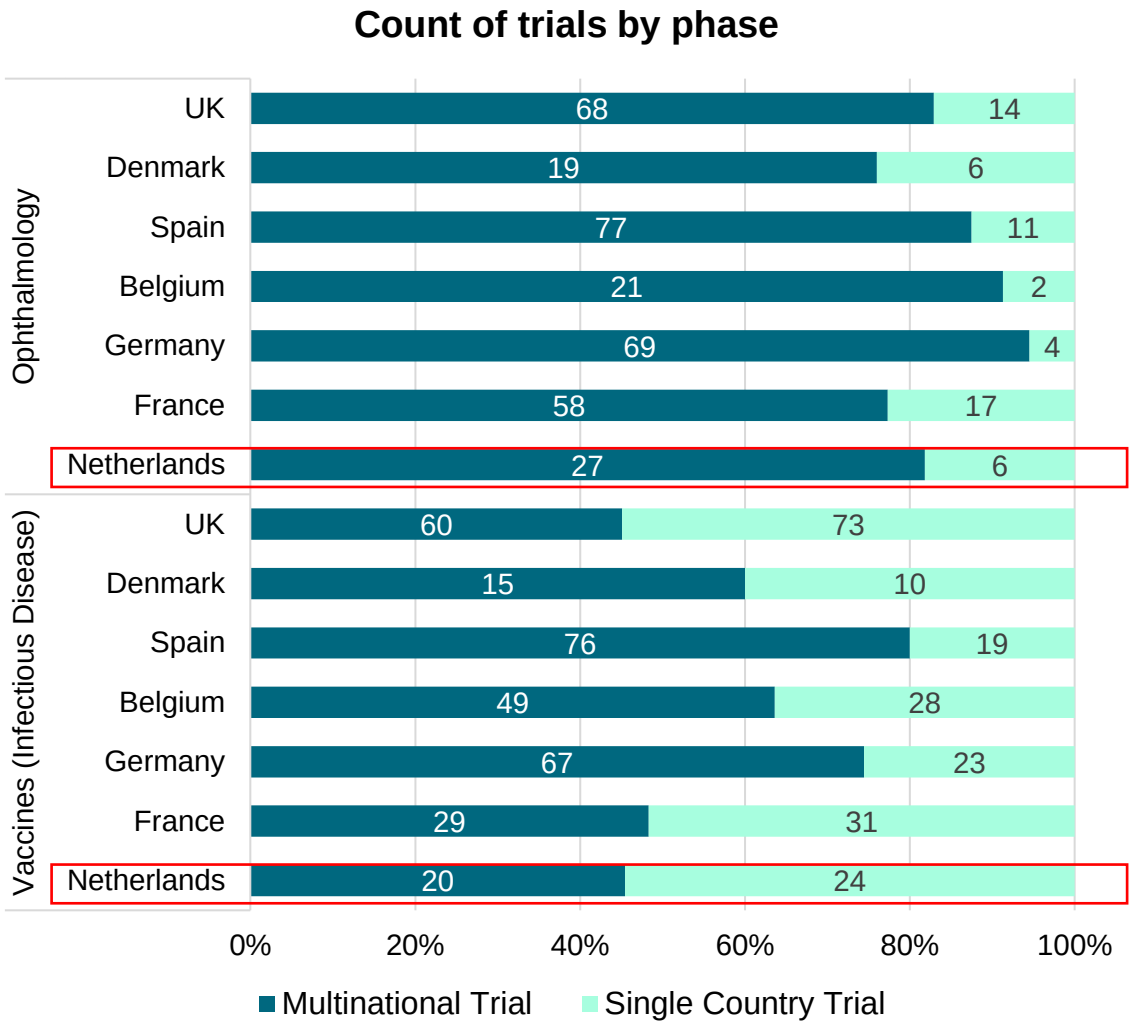


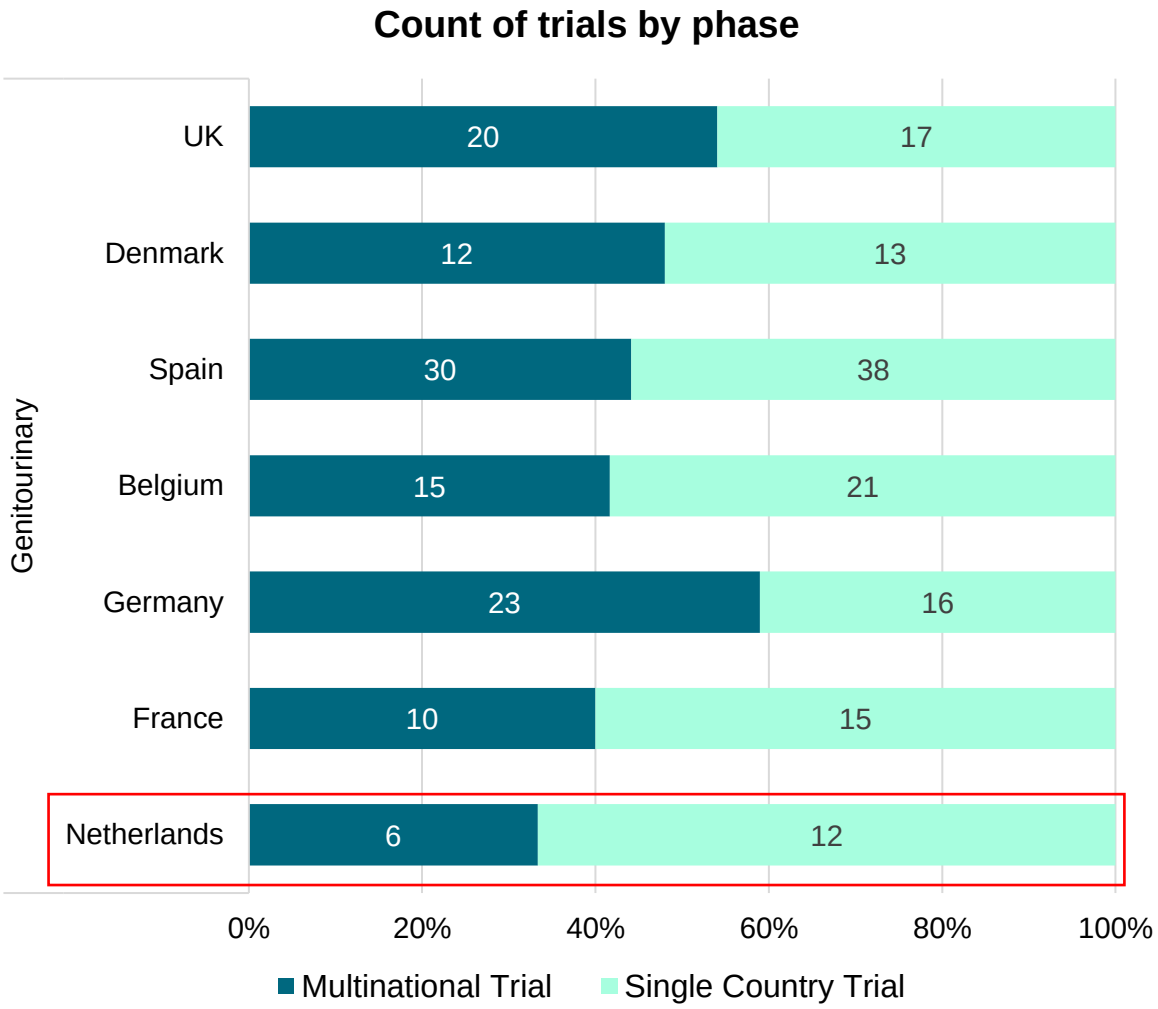


Sources: Citeline| Trialtrove N.B: Data labels are raw values

Proportion of trials in each TA by single-country vs multinational (2/2)

Relative to other therapeutic areas, genitourinary, infectious disease, and vaccine (infectious diseases) trials tend to have a greater proportion which are located in a single-country





'Unassigned' removed from charts

Sources: Citeline| Trialtrove N.B: Data labels are raw values

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
Encouragement of enterprise and innovation in life science	• The Netherlands lists life sciences and health among their top nine sectors. • 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

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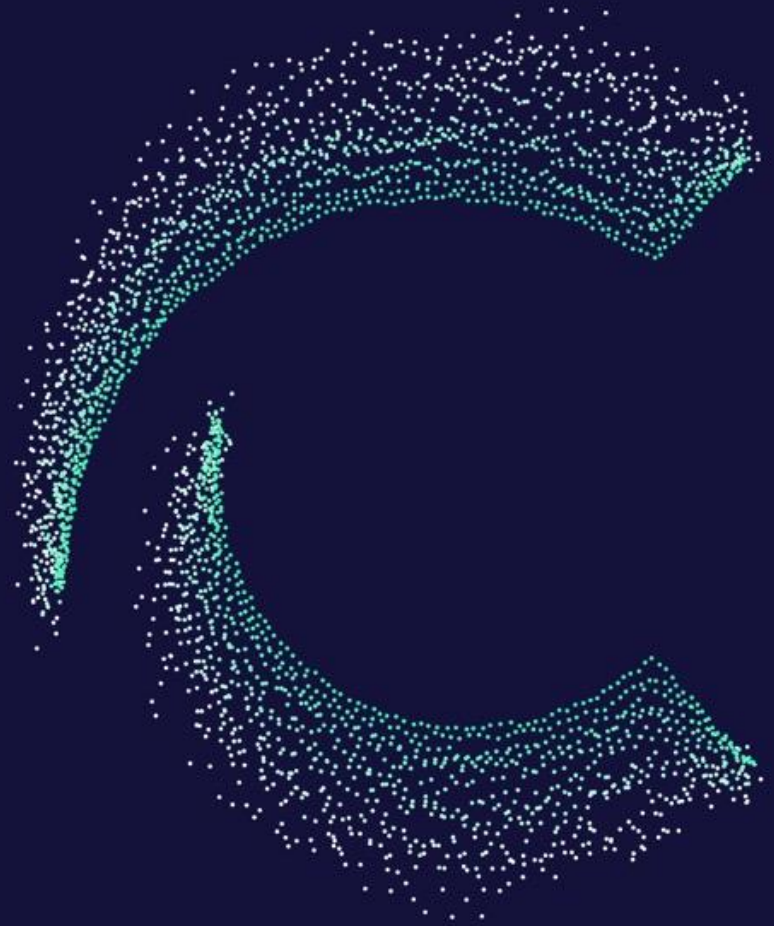
Factors Impacting Site Selection

4.1 Academic Excellence



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SWOT analysis – academic excellence

Scientific leaders in the Netherlands have a record of first-class research, the country's cardiology KOL networks have been cited by a Big Pharma key player as helping the Netherlands stand out from other countries for this TA

Strengths

- High-quality scientific community with great presence at conferences and in papers
- Above average Scimago H-index ranking in Geriatrics and Gerontology, and Rheumatology
- Collaboration between academic centres and networks
  - WCN and VRN make the country particularly attractive for cardiology research

Weaknesses

- Limited numbers of academic sites means that, largely for early-stage trials, industry is often competing with academia for these sites
- Shortage of scientific knowledge according to the Skills Need Indicator

Opportunities

- Using good communication of scientific experts to strengthen industry collaboration
- Reducing the bureaucracy in academia could allow academia to focus more on innovation

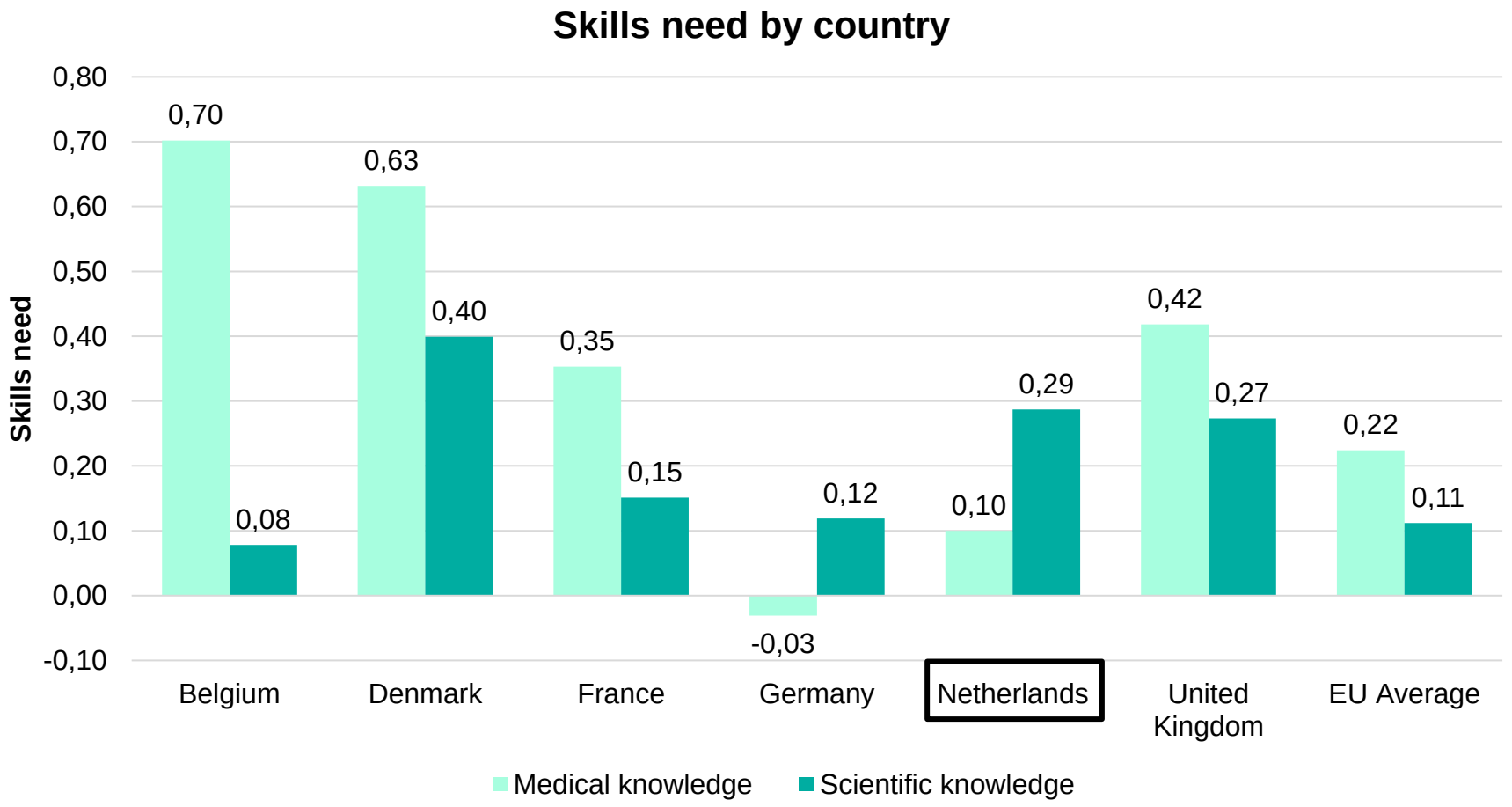
Threats

- Potential shortage of nurse practitioners on wards

Sources: Citeline| Trialtrove; Citeline Primary Research; Scimago Country Ranking, 2021

Scientific and medical skills need by country

According to the OECD Skills Need Indicator, the Netherlands has the second lowest shortage of medical expertise after Germany; however, the Netherlands has the second highest shortage of scientific knowledge



The Skill Needs Indicators provides an overview of the shortages and surpluses of skills across countries.

Positive values indicate skill shortage, while **negative values point to skill surplus**. The larger the absolute value, the larger the imbalance. The value of 1 represents the largest shortage and the value of -1 the largest surplus across OECD countries..

Medical knowledge is comprised of knowledge in medicine, dentistry, psychology, therapy and counselling. Scientific knowledge is comprised of knowledge in biology, chemistry, physics, sociology and anthropology.

The data refer to 2019, with the following exceptions: 2018 for France and 2017 for Germany and the UK.

*"Focus on more traineeships for nurses, because somebody has to do the work." –**Key player 5***

Source: OECD. Key players were interviewed for their insights, n=6

Comparison of Netherlands to other EU countries

Key players recognised the Netherlands' academic excellence relative to other EU countries, citing collaboration, high-quality research institutes, scientific leaders, and conference participation as relevant factors

Ease of collaborating with academics

Key player 1: Netherlands can move quickly relative to France and Germany

Key players 4 and 2: Netherlands is more readily available for collaboration

Scientific expertise

Key player 3:

- Netherlands has a higher density of global scientific leaders
- The Netherlands is ahead of other countries in cardiovascular and paediatric oncology (largely thanks to the Princess Maxima Medical Centre)
- Immunology leaders are also a strength and have the in-house capabilities for clinical trials

Key player 6: does not believe there is an advantage of academic excellence in the Netherlands compared to the comparator EU countries

Rank	Key player 1 (Ranking is from an Alzheimer's perspective)	Key player 3 (Only ranked Netherlands)	Key player 4
1	UK	**Netherlands**	France
2	**Netherlands**	*Netherlands is at no.1. The first time I was at ESMO, I was so impressed by the number of Dutch investigators that were on the stage or on papers. That's also what makes it easy for me to attract clinical research from an American-based company." – **Key player 3***	UK
3	France		Belgium
4	Germany		**Netherlands**
5	Belgium		Germany
6	Denmark	*"The Netherlands, I would rank high [having very prominent research institutes]." – **Key player 1***	Denmark

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

Ranking of the major sites within therapeutic area

Erasmus MC's high overall ranking is driven by oncology trials, while Amsterdam UMC ranks high in other large indications

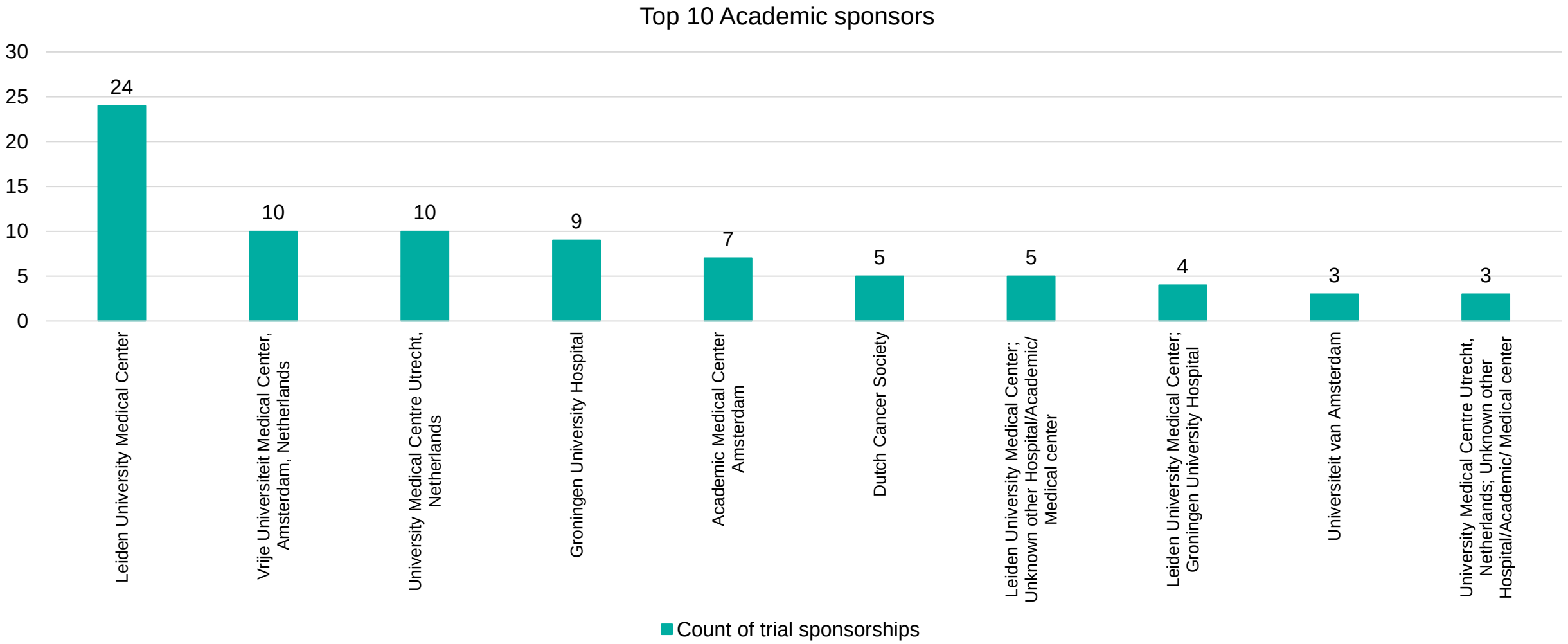
Number of trials conducted in each TA (decrease)

Top Sites Running Clinical Trials in Netherlands	Total Trials Initiated 2018-2022	Total Trials Ongoing	Oncology	Autoimmune & inflammation	Cardio-vascular	Metabolic & Endocrine	CNS	Infectious Disease	Ophthal-mology
Erasmus MC	412	349	1	2	5	3	5	2	/
Amsterdam UMC - Locatie AMC	320	260	9	1	1	1	7	4	2
Universitair Medisch Centrum Groningen (UMCG)	288	226	3	4	2	2	8	6	4
Universitair Medisch Centrum Utrecht (UMC Utrecht)	288	235	5	3	6	4	2	3	9
Radboud Universitair Medisch Centrum (Radboudumc)	282	217	6	5	3	5	6	1	1
Leids Universitair Medisch Centrum (LUMC)	234	200	8	6	8	7	1	5	5
Amsterdam UMC - Locatie VUMC	216	212	4	7	7	6	10	/	6
Antoni van Leeuwenhoek Ziekenhuis (NKI-AVL)	207	190	2	/	/	9	/	/	/
Universiteit Maastricht (UM)	196	174	7	10	4	8	/	/	10
Amphia Ziekenhuis	90	/	10	/	10	/	/	7	/

Sources: Citeline| Sitetrove

Top 10 academic sponsors in the Netherlands – single-country trials

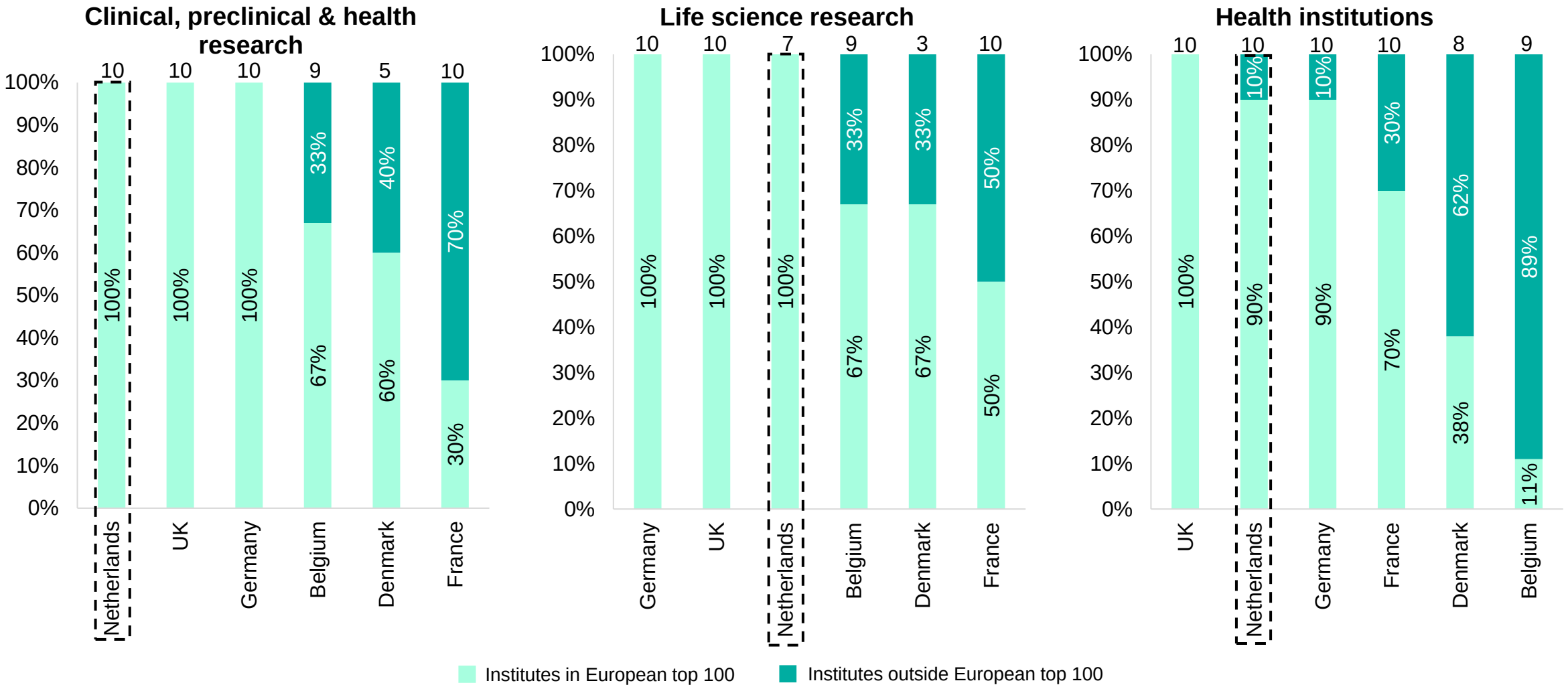
Leiden University Medical Center leads in academic trial sponsorship in the Netherlands, appearing 3 times in the top 10 sponsor list as a stand-alone sponsor and in collaboration with other institutions



Sources: Citeline| Trialtrove; N.B: All trials with at least one academic sponsor

Top research and health institutes

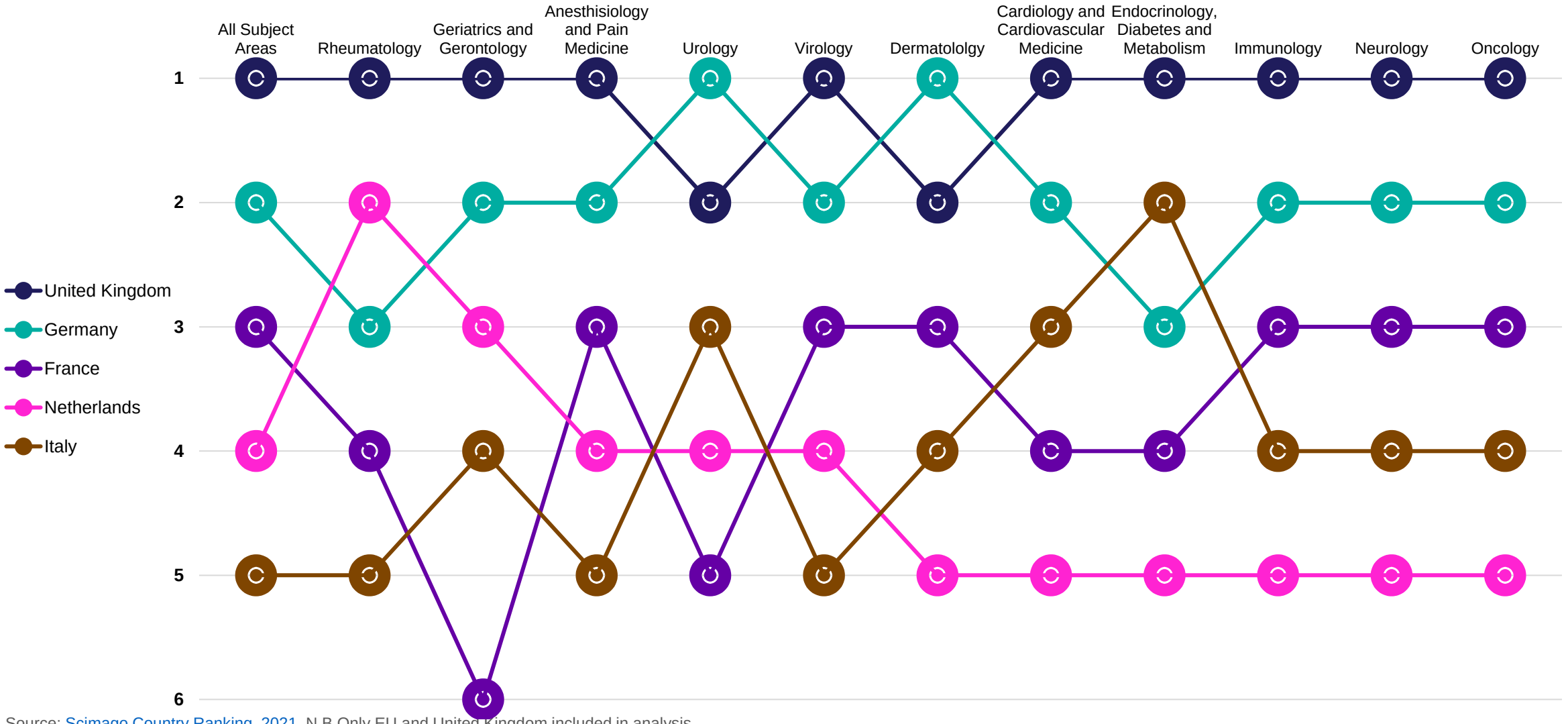
100% of the Netherlands' top 10 institutes for clinical, preclinical & health research have scored in the EU top 100 - this same proportion is seen for the country's 7 assessed life science research institutes



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

H-index ranking by subject area, 2021

In 2021, the Netherlands ranked 4th overall in the EU for impact of scholarly output, scoring higher than its average in Rheumatology and Geriatrics and Gerontology

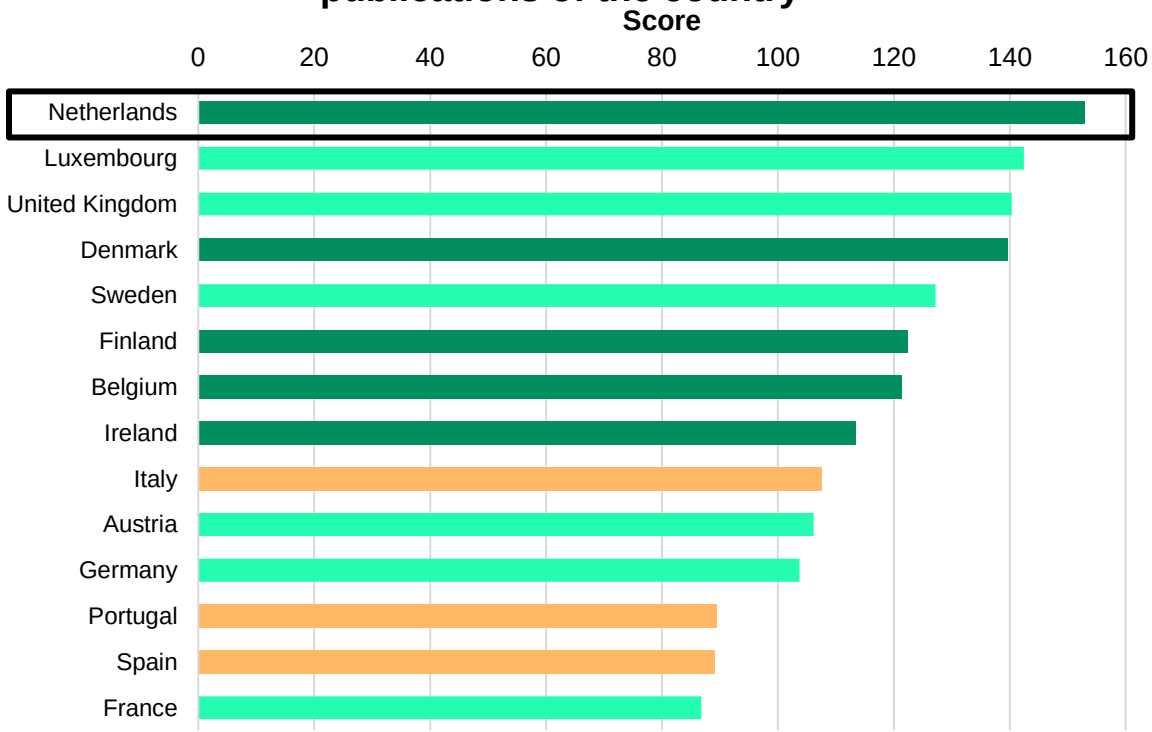


Source: Scimago Country Ranking, 2021, N.B Only EU and United Kingdom included in analysis

European Innovation Scoreboard, 2022

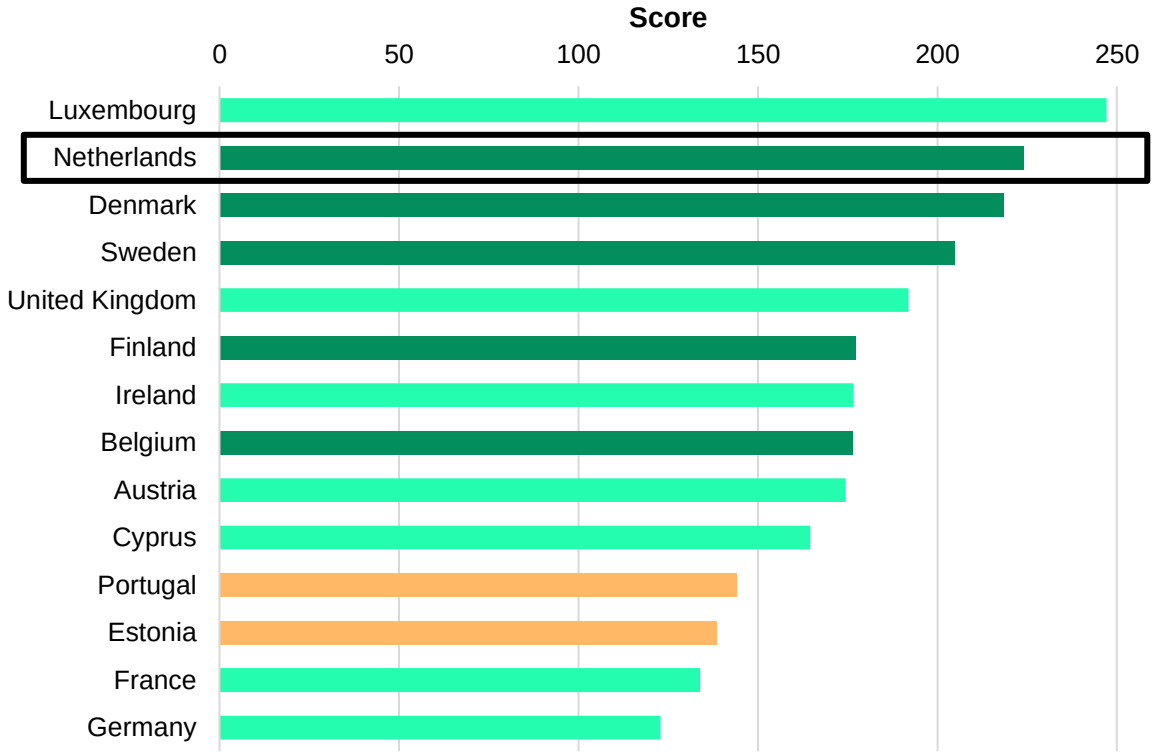
The Netherlands has the greatest proportion of its publications occupying the top 10% most cited worldwide and ranks second in Europe as an ‘Innovation Leader’ for the attractiveness of its research systems

Scientific publications among the top 10% most cited worldwide as a percentage of total scientific publications of the country



Top 10% most cited publications is a measure for the efficiency of the research system, as highly cited publications are assumed to be of higher quality. Data on the percentage share of publications among the top 10% most cited publications are for 2011-2018. Data have been calculated using fractional counting and have been extracted from Scopus.

Attractive research systems



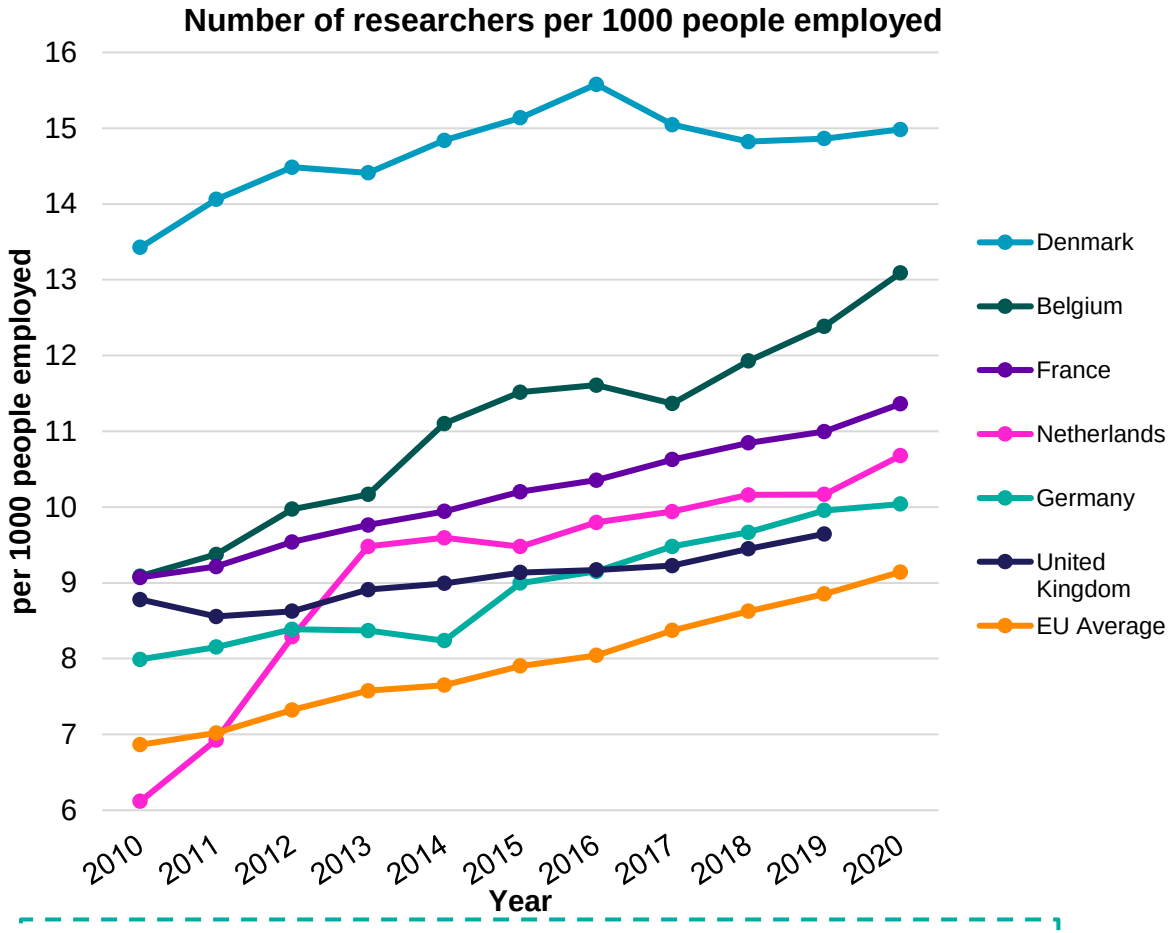
Attractive research systems includes three indicators and measures the international competitiveness of the science base by focusing on international scientific co-publications (2021), most cited publications (2019), and foreign doctorate students (2020).

Innovation Leader Strong innovator Moderate innovator

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

Researchers per 1000 people employed, and highly cited researchers

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, taking 2.9% of the world share



Researchers are defined as science and technology professionals engaged in the conception or creation of new knowledge, products, processes, methods and systems, as well as in the management of the projects concerned

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

*"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."– **Key Player 3***

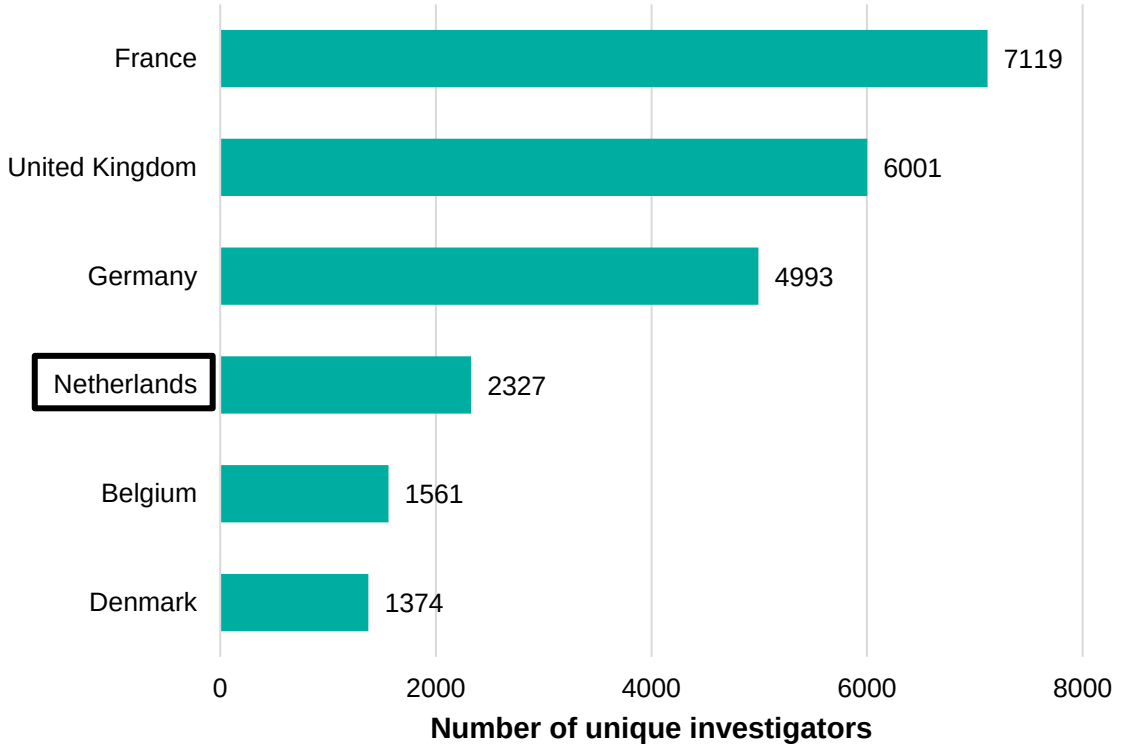
Highly Cited Researchers have shown substantial influence through multiple top 1% cited papers in sciences and social sciences journals from 2011 to 2021. The list focuses on contemporary research achievement in the Web of Science Core Collection.

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

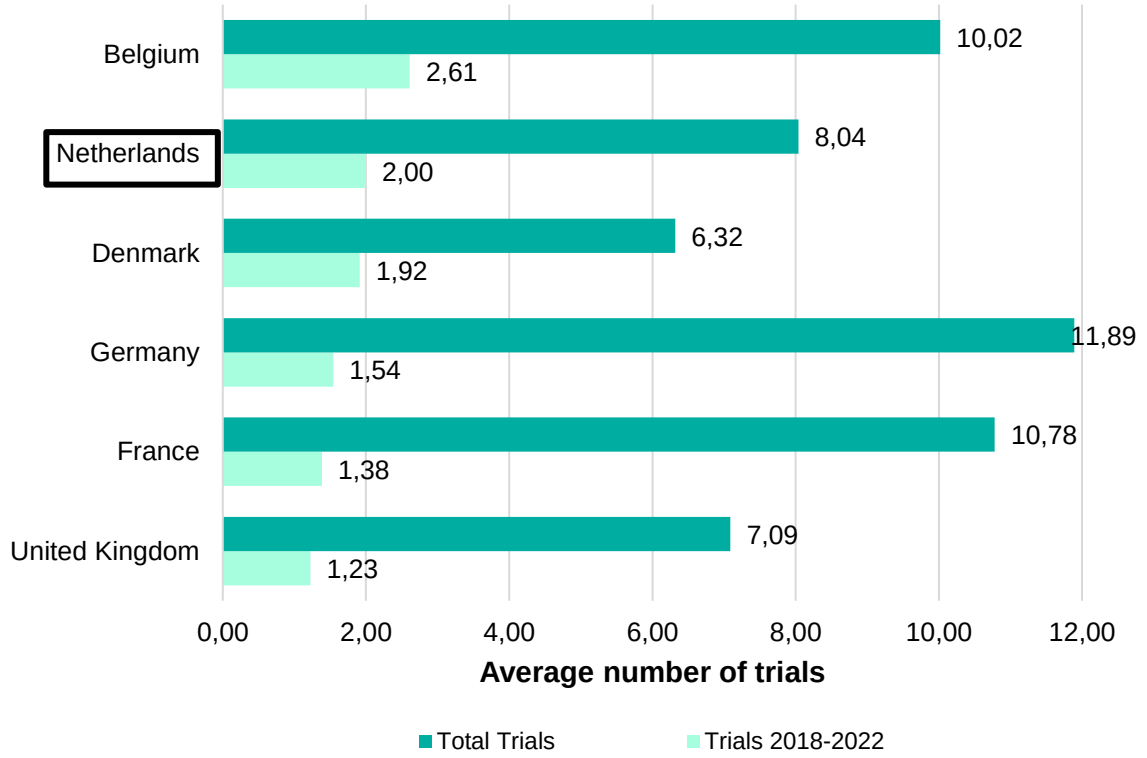
Number of trials per investigator, 2018-2022

Despite having fewer investigators, the Netherlands ranked second among comparators from 2018 to 2022, averaging two trials per investigator. On average, Dutch investigators participate in 8 trials during their career

Unique investigators involved in trials initiated 2018-2022



Number of trials per investigator



Investigators associated with clinical trials are captured in Sitetrove provided that following inclusion criteria are met:

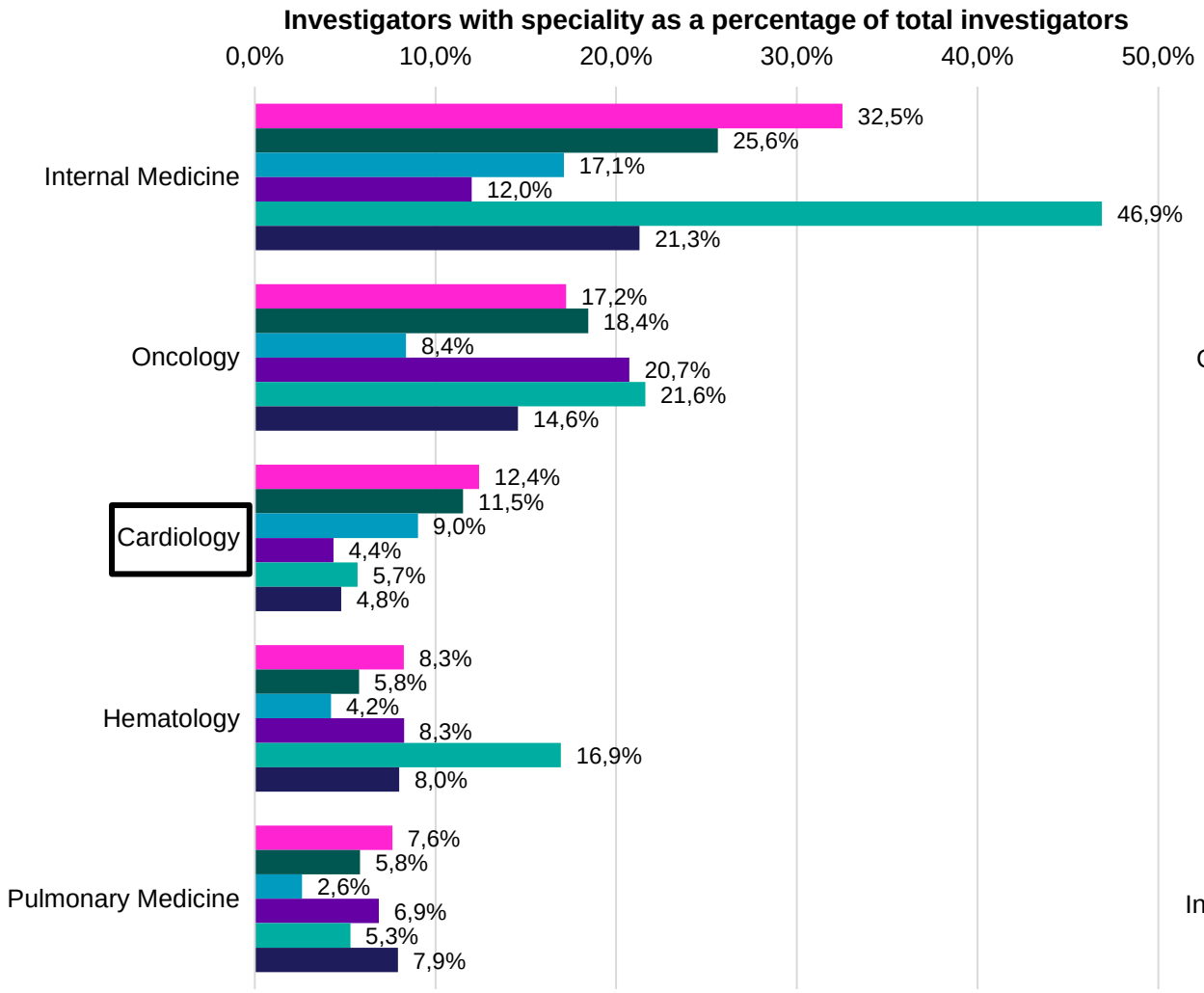
- The investigator is credentialed to treat patients.
- The investigator can recruit patients.
- The investigator is located at a site that will see and treat patients.
- The indication falls within our portfolio and the trial involves a pharmacological intervention.

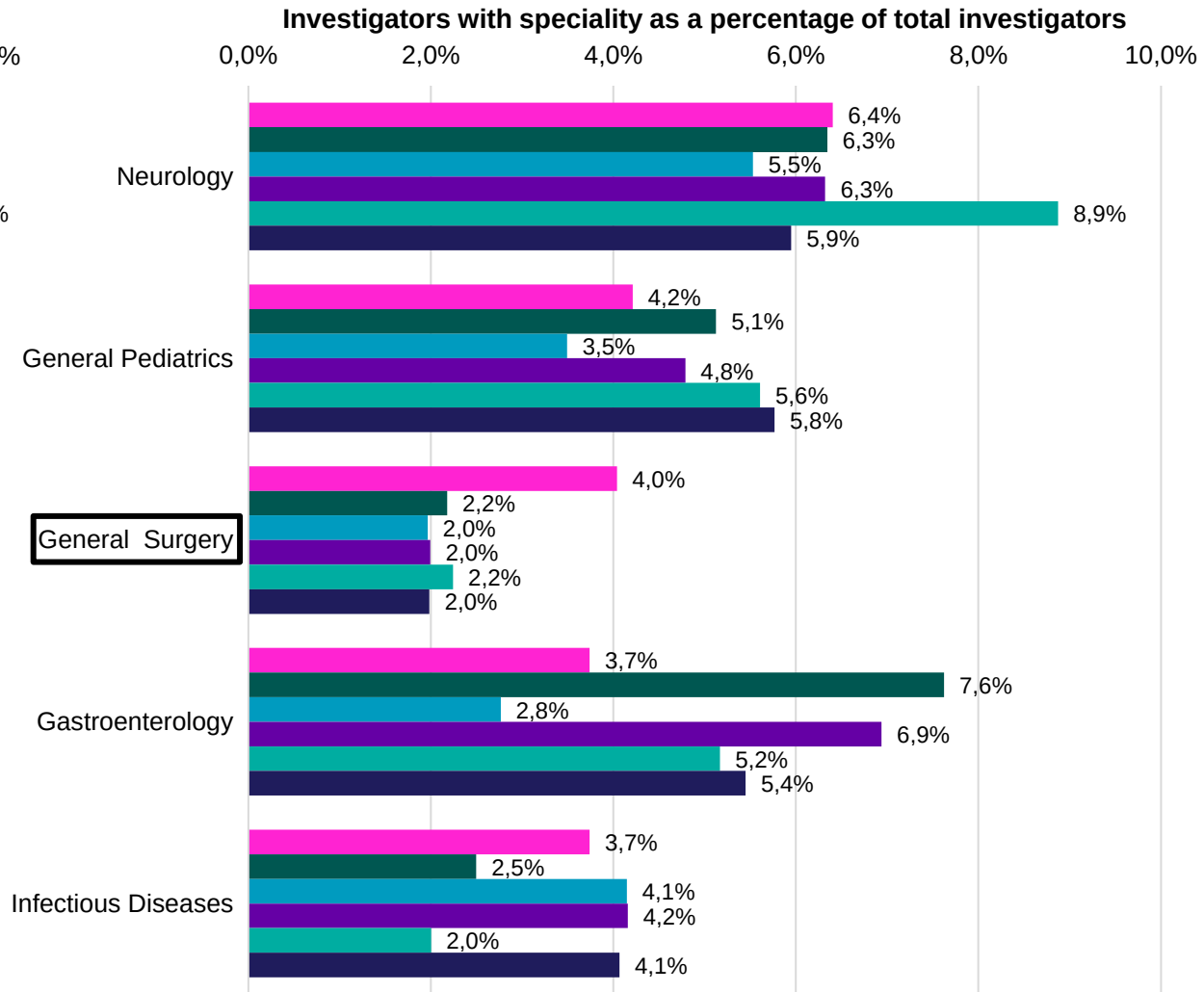
Inclusion Criteria
Trial Start Date; 01/01/2018-31/12/2022
Trial Status: Ongoing, Terminated, Completed
Exclusion Criteria
Study Keywords: NOT 'Observational' OR 'Non-interventional'
For specialty table 'NA/Other' was removed

Source: Citeline|SiteTrove

Investigator specialities, 2018-2022

In trials initiated between 2018 and 2022, the Netherlands had the highest proportion of investigators specialising in Cardiology and General Surgery when compared to comparator countries





Source: Citeline|SiteTrove

Netherlands Belgium Denmark France Germany United Kingdom

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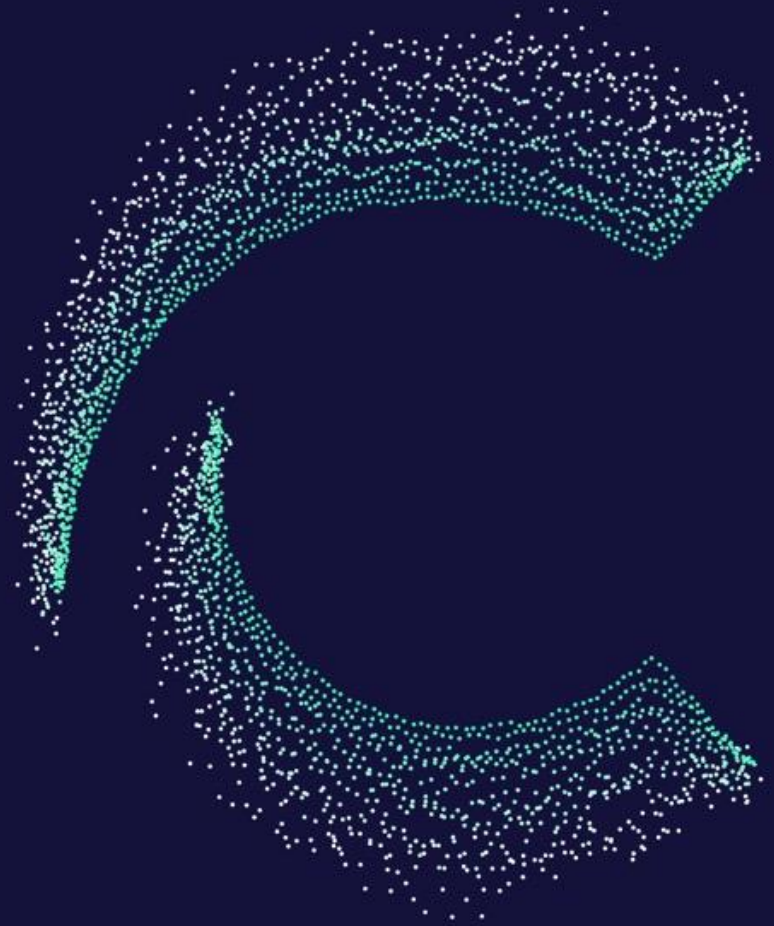
Factors Impacting Site Selection

4.2 Ease of Conducting Clinical Trials



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SWOT analysis – ease of conducting clinical trials

Willingness to collaborate and a high number of research networks provides the Netherlands with an advantage, however clinical trial costs and patient mistrust of industry need to be addressed

Strengths

- Clinical trial stakeholders are easy to access and open for collaboration
  - High density of hospitals in Randstad region means communication and travel between trial stakeholders is quick
  - It is easy to receive feedback from regulatory agencies
- 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

- Patients have low awareness of clinical trials and are nervous towards working with industry due to a level of mistrust towards Pharma companies
- Cost of clinical trial start-up can create a bottleneck – greater communication and transparency is needed at an earlier stage on what the costs for sponsors will be

Opportunities

- Spending on health and R&D (both as a percentage of GDP) was on the rise from 2019-2021
- Despite the ECTR harmonizing trial approval procedures, the Netherlands has the opportunity to stand out by, for example, focusing on increasing the speed of ethics approval, and collaborating with other countries

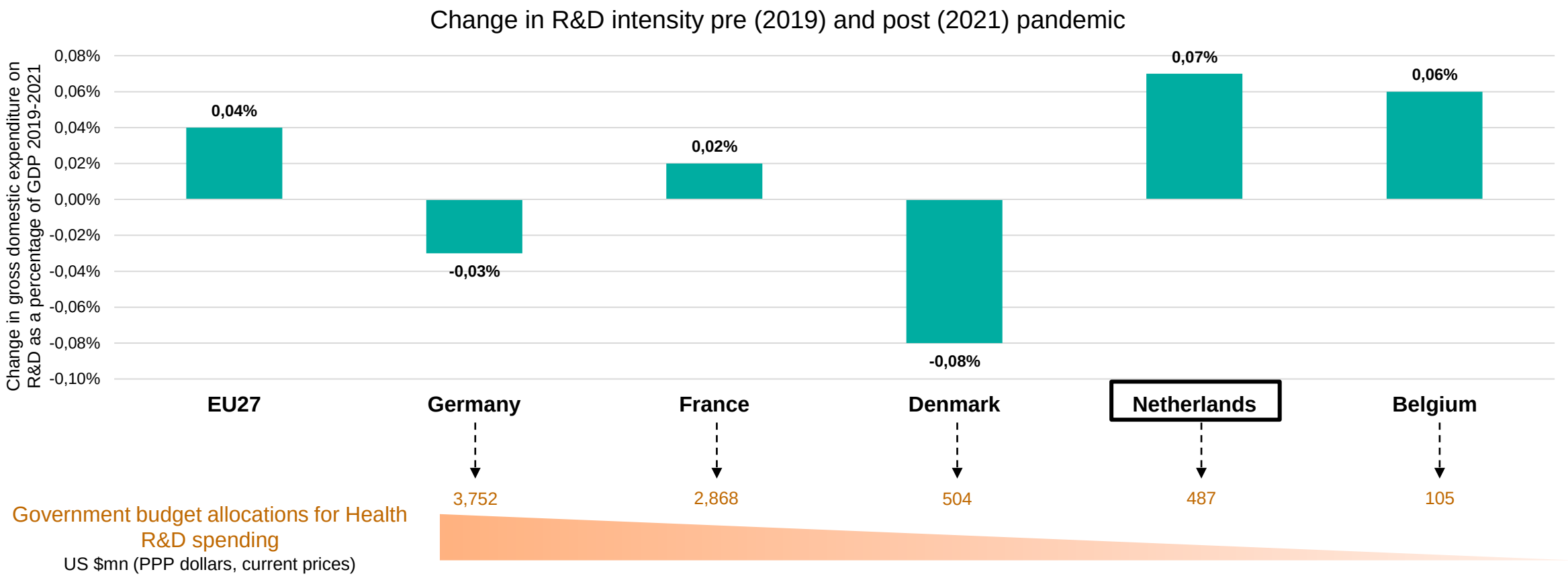
Threats

- Although investment into R&D and healthcare infrastructure is high, the number of hospital beds is on a decline
- The Netherlands has a relatively high number of ATMP trials relative to population size, but hindrances to access, such as the ‘lock’ could pose a barrier to their use

Sources: Citeline| Trialtrove; Citeline Primary Research

R&D intensity in comparator countries, and budget allocation

Netherlands has seen the greatest change in science and technology R&D intensity between 2019 and 2021, surpassing the EU27 average and suggesting investment in future innovation



In 2020 the Dutch Government allocated the second smallest budget among comparator countries toward Health R&D specifically

Source: OECD, UK Parliament, Research and development spending: Pharmaceuticals, 2022

The percentage of trial budget allocation in the Netherlands

Key player insights: Pharma companies allocate substantially more budget to multinational trials than to single-country trials

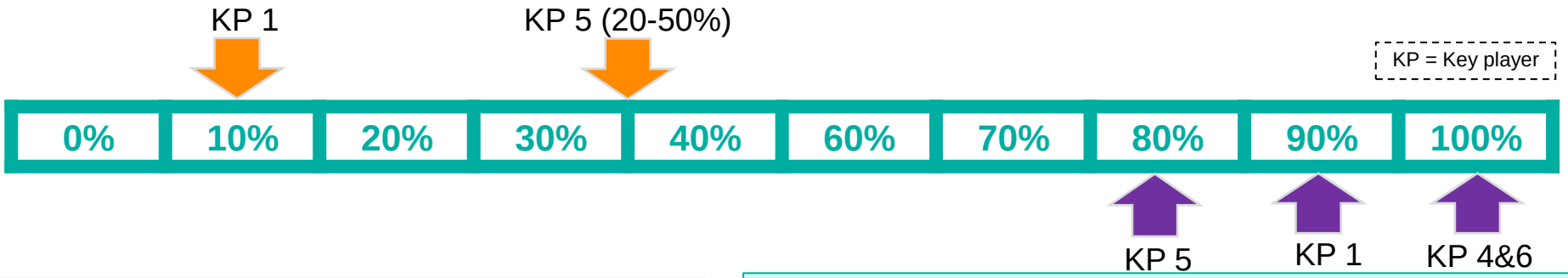
Single-country trials

- Key players believe that in the Netherlands, single-country trials account for only a **minority** of trials run by CROs, and approximately 8% by pharmaceutical companies
- Single-country trials generally are relatively **small** trials, so the budget allocation is lower than for multinational trials

*"Organisations such as CHDR in Leiden run single-site or single-country trials" – **Key player 1***

*"We don't do single-country trials in the Netherlands, only multi-national. For single country it's China, US, and Japan." – **Key player 4***

Percentage of budget



Multinational trials

- Multinational trials are the **primary focus** of pharmaceutical companies
- In selected indications, the Netherlands has been chosen as the trial country in about 1/5 of multinational studies; thus the correlated budget allocation for the Netherlands

*"For countries like the Netherlands, Belgium, Denmark, and Austria, we are asked to focus on what we are doing rather than recruiting for every study. We select studies where we can contribute, and our budget would correlate to the number of studies" – **Key player 3***

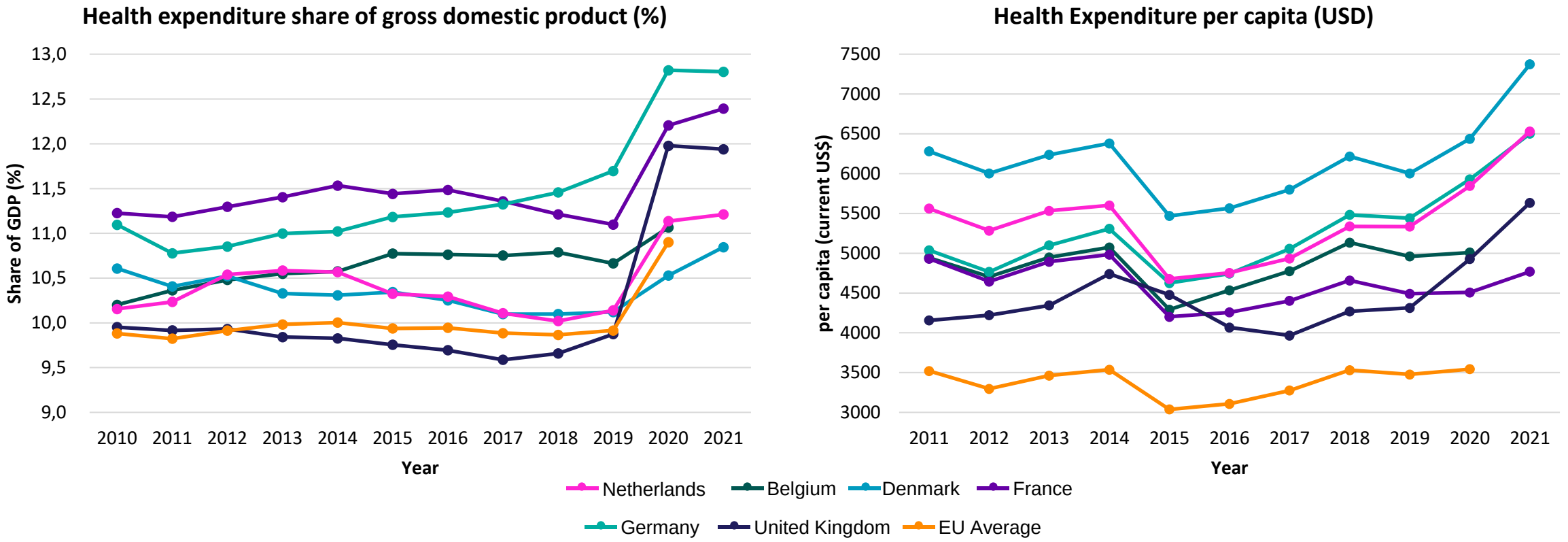
*"For bigger countries, such as France, Germany and the UK, the number of studies is 5 times more than the Netherlands, thus the budget." – **Key player 3***

*"For early oncology, especially haematology, about 15-20% of studies in the Netherlands have been selected as a multi-country partition." – **Key player 4***

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

Health expenditure in 6 comparator countries

Similarly to the trend in R&D spending, health expenditure has also seen a sharp uptick since 2019



For the Netherlands, the sharp rise in health expenditure seen after 2019 will at least in part be due to the Government allocating additional revenue to compensate for increased spending due to COVID in 2020 and 2021

Source: World Bank, OECD, KPMG Site Selection for Life Sciences Companies in Europe, 2018 Edition

Global healthcare rankings of the Netherlands

The Netherlands is rated highly both from a public heath and healthcare system point of view, ranking 11th in the world for both measures

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 **Legatum Prosperity Index** 'Health' pillar measures the extent to which people are healthy and have access to the necessary services to maintain good health, including health outcomes, health systems, illness and risk factors, and mortality rates. The 'Health' pillar is comprised of behavioral risk factors (10%), preventative interventions (15%), care systems (15%), mental health (15%), physical health (20%) and longevity (30%)

The **Health Care Index** by CEOWORLD is an analysis of the overall quality of the health care system, including health care infrastructure; health care professionals (doctors, nursing staff, and other health workers) competencies; cost (USD p.a. per capita); quality medicine availability, and government readiness. It also takes into consideration other factors including environmental, access to clean water, sanitation, government readiness on imposing penalties on risks such as tobacco use, and obesity. The ranking takes 89 countries around the world into consideration.

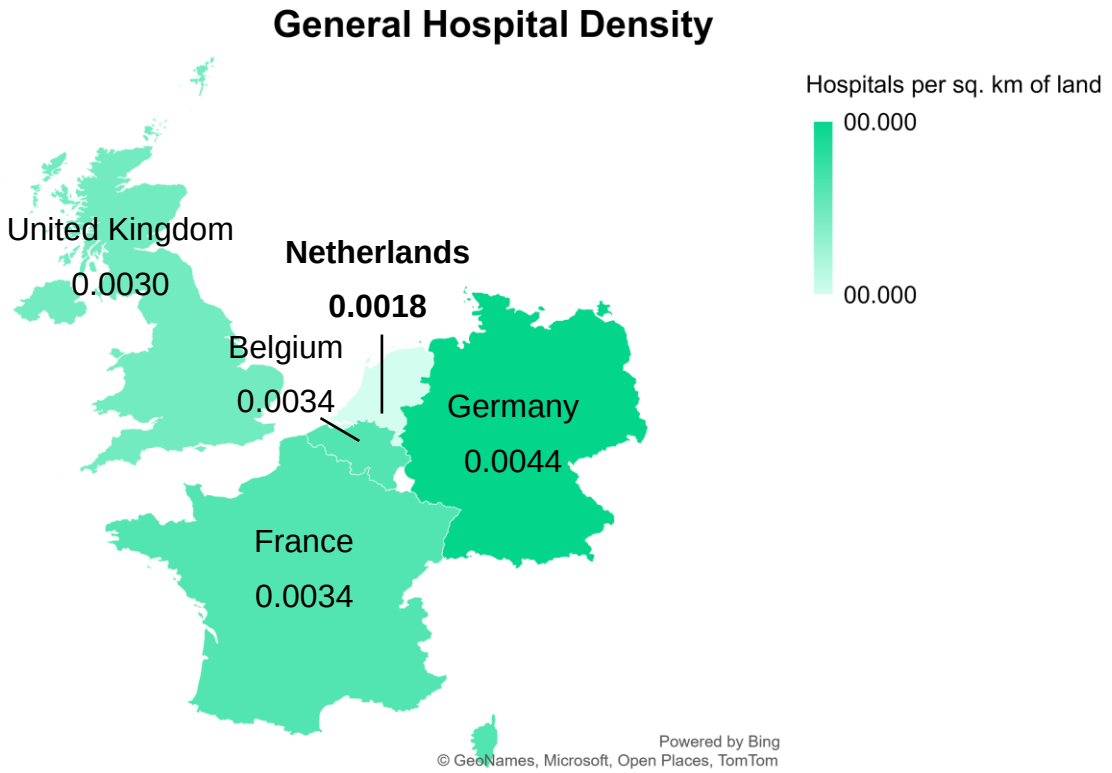
Source: The Legatum Prosperity Index, Legatum Prosperity Index Methodology, CEOWORLD

Number and Density of General Hospitals per Country

In comparison to other benchmark countries, the Netherlands has a lesser number of general hospitals

Country	Number of General Hospitals (2020)	General Hospitals per sq. km of land area (2020)
France	1868	0.0034
Germany	1558	0.0044
United Kingdom	727	0.0030
Belgium	104	0.0034
Netherlands	**75**	**0.0018**

Source: OECD



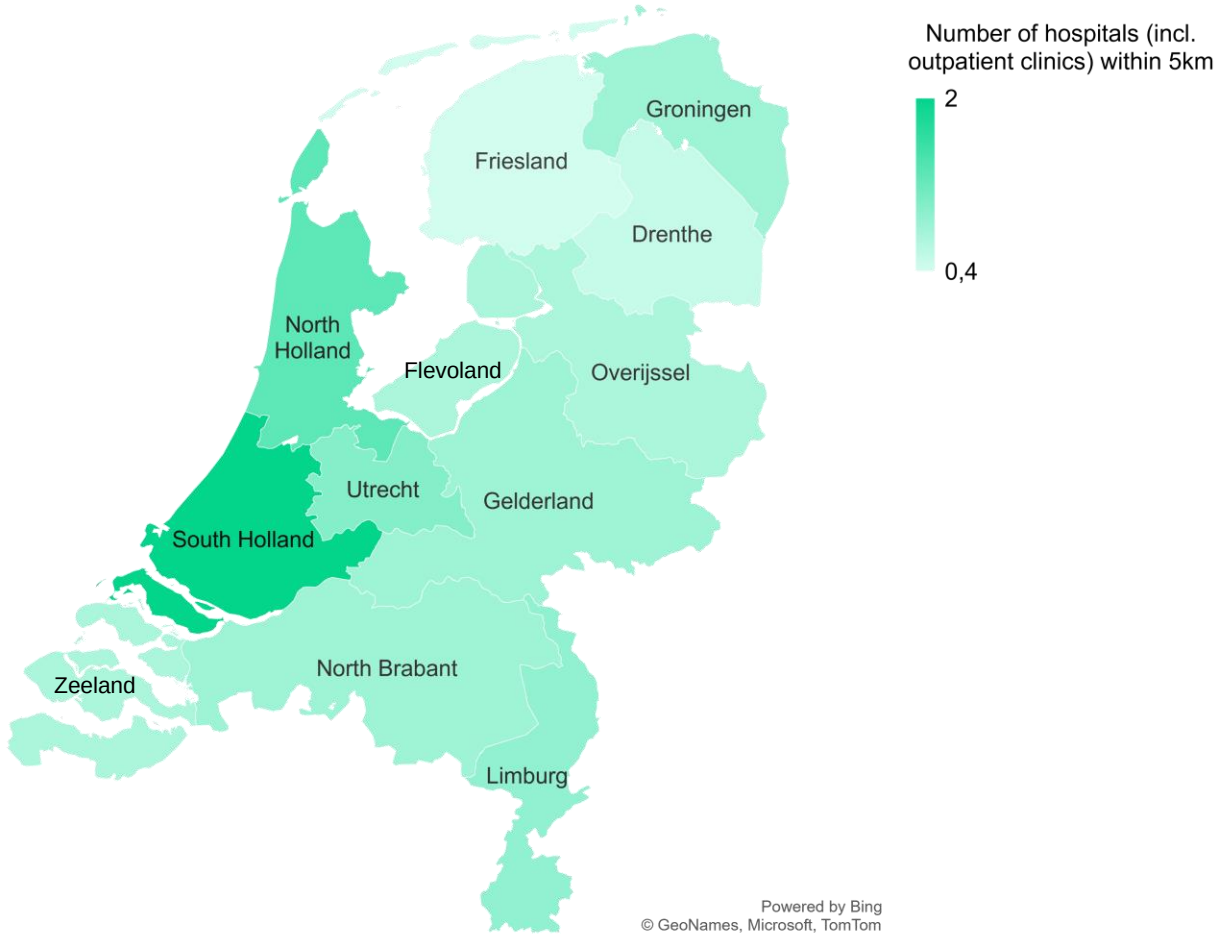
Inclusion
- Community, county, and regional hospitals (other than specialised hospitals)
- General acute care hospitals
- Army, veterans, prison and police hospitals if settled in a separate establishment (other than specialised hospitals, e.g., forensic hospitals)
- Teaching hospitals, university hospitals (other than specialised hospitals)
- General hospitals run by private companies if set up as a separate independent establishment
- General hospitals of private non-profit-organisations (e.g., Red Cross or Red Crescent) (other than specialised hospitals)
- Integrated Community health care centers primarily engaged in inpatient service.

Proximity to hospitals, 2022

On average, there is 1 hospital within 5km in the entire country, with a larger density in the Randstad region, which encompasses Utrecht, Flevoland, North- and South-Holland

Province	Number of hospitals Within 5 km (2022)
South Holland	2
North Holland	1.3
Utrecht	1.0
Limburg	0.9
Groningen	0.8
Gelderland	0.8
North Brabant	0.8
Overijssel	0.7
Flevoland	0.7
Zeeland	0.7
Drenthe	0.5
Friesland	0.4
Netherlands (Average)	**1.1**

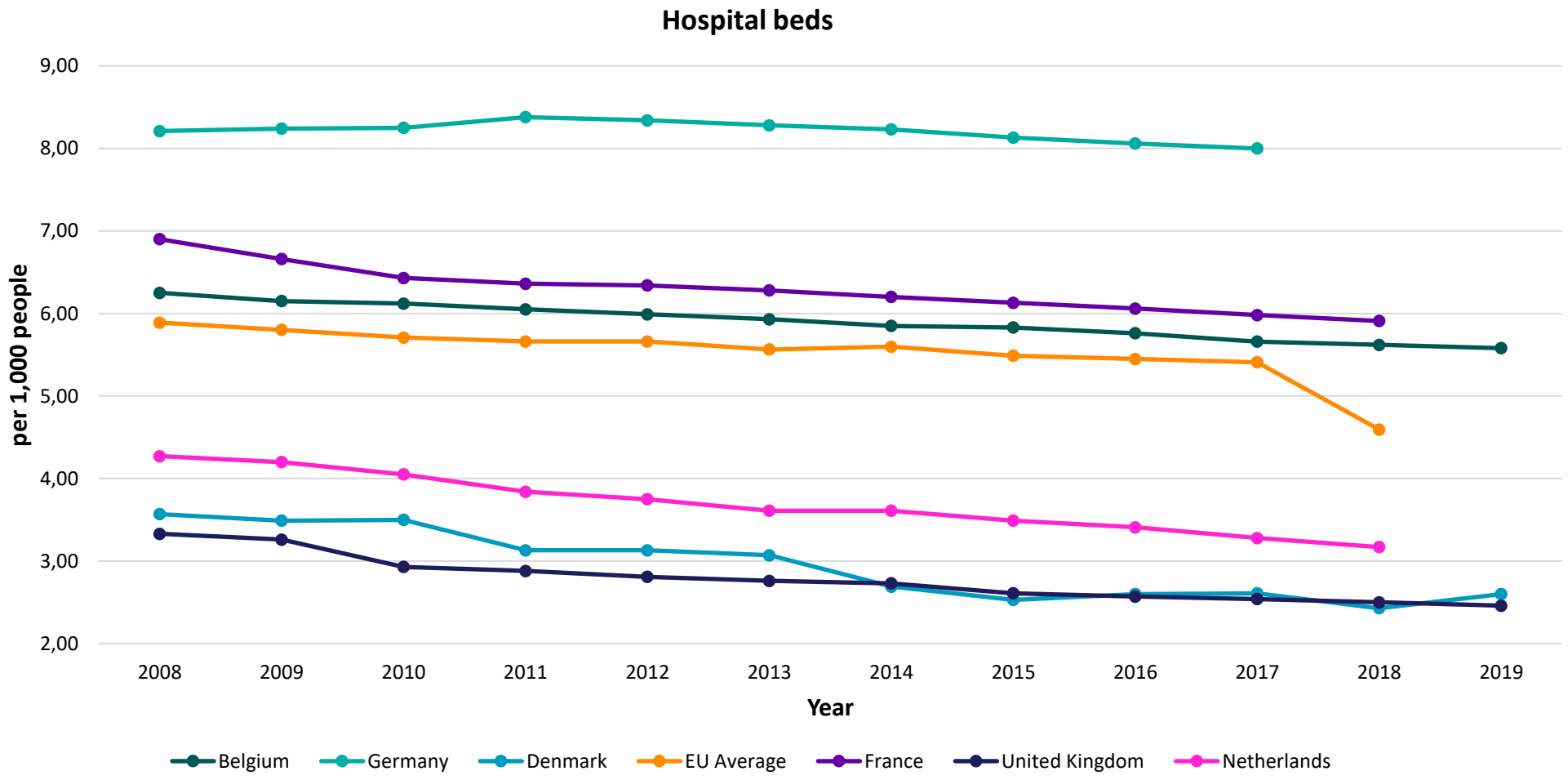
Number of hospitals (incl. outpatient clinic) within 5km



Source: Statistics Netherlands

Hospital beds

The number of hospital beds per 1000 people has steadily been declining across the EU, and the Netherlands has historically followed this



Source: World Bank

Organisation of care

In the Netherlands, access to medicine is eased through centralised institutional care; additionally, basic health coverage is provided by multiple mandatory health insurance funds

Country	Main Source of Basic Health Coverage	Mandatory Health Insurance	Centralised or Decentralised ?
Netherlands	**Multiple health insurance funds or companies**	**Yes**	**Municipalities have new responsibilities in the domains of youth care, long-term care and income support. Institutional care remains a central government task**
Belgium	Multiple health insurance funds or companies	Yes	The Belgian healthcare system is mainly organised on the federal and regional level
Denmark	National health system (including those with distinct localised services)	No - free public healthcare	Primarily decentralized health system, the national government provides block grants from tax revenues to the regions and municipalities, which deliver health services
France	National health system	Yes	France has maintained one of the most centralized health policy systems in Europe
Germany	Multiple health insurance funds or companies	Yes	Highly decentralized, with 16 municipalities (called Länder) sharing responsibility with the government for hospital planning, building and the upkeep of technical facilities
UK	National health system (including those with distinct localised services)	No – largely free public healthcare at the point of delivery	NHS is highly centralised

Source: Please see notes

Clinical trial approval process: pre-ECTR

Data from a sample of ATMP trials suggest timings have been competitive for that therapy subset relative to comparator EU countries, although awareness of this speed potential among key players is limited

Pre-ECTR Process

Actual average authorisation time of 152 days

Regulated by **Medical Research Involving Human Subjects Act (WMO)**

Review and approval **by Medical Research Ethics Committee (MREC)**

60 days

Approve of composition and operating procedures of the MRECs

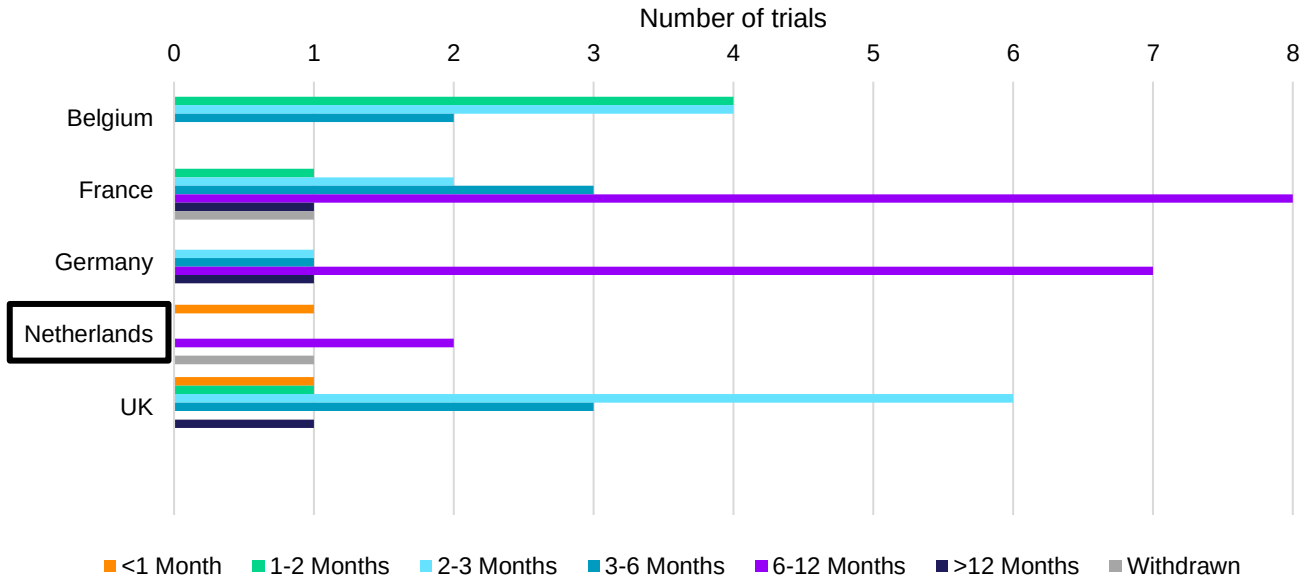
Marginal review and approval **by Central Committee on Research Involving Human Subjects (CCMO)**

14 days

90 days

Review and approval by **Medicines Evaluation Board (MEB)**

ATMP Clinical Trial Approval Times
(N=26 ATMP Clinical Trials, 18 of which were multinational)



The Netherlands is currently one of two countries in which ATMP trials have been approved in less than 30 days, but there seems to be a lack of awareness of how competitive the Netherlands' ATMP trial approval speed can be:

- **Only 1 in 6 key players were aware of this fact**
- According to respondents of a separate ARM survey, GMO approval is particularly long in the Netherlands and has caused withdrawal of a clinical trial application in the country

Source: Allucent, NCBI - Di Martino S, CCMO; N.B. Process chart is not exhaustive; Alliance for Regenerative Medicine; N.B. Denmark was not included in original analysis; Citeline primary research

Clinical trial approval process: post-ECTR

The introduction of the ECTR was intended to harmonize and streamline trial approvals across the EU; however key players are yet to see reduced timelines

Post-ECTR

Intended maximum authorisation time of 106 days

National clinical trials office at validates application dossiers and assigns MREC or CCMO for single country trials. In multinational trials **reporting Member State** validates dossiers.

max. 25 days

MREC or CCMO review part 1 (technical, scientific, and clinical quality) – Joint assessment by each concerned member state (if multinational trial), with one conclusion valid for all

MREC or CCMO review part 2 (local feasibility and patient information documentation) – Assessment by each member state individually

max. 76 days

max. 126 days

Key:
Exceptions for instance trials that require special expertise such as gene or somatic cell therapy

Implications of the ECTR for the Netherlands

Could promote **collaboration**, patient **participation**, and positive **intentions** (n=1 Key player)

No impact (n=1 Key player)

The ECTR causes trial **delays/challenges**, and the strict timelines with be a hurdle for researchers (n=4 Key players)

2 key players mentioned the lack of initial benefit could be down to teething problems as the ECTR is relatively new

How to stand-out to sponsors in the context of this harmonisation

1. Focus on faster ethics approval timelines at hospital level
2. Collaborate with other players in the field
3. Ensure that documents are ready prior to CTIS approval for short 'First Patient In' times
4. Be willing to have conversations outside of the system – maintaining flexibility

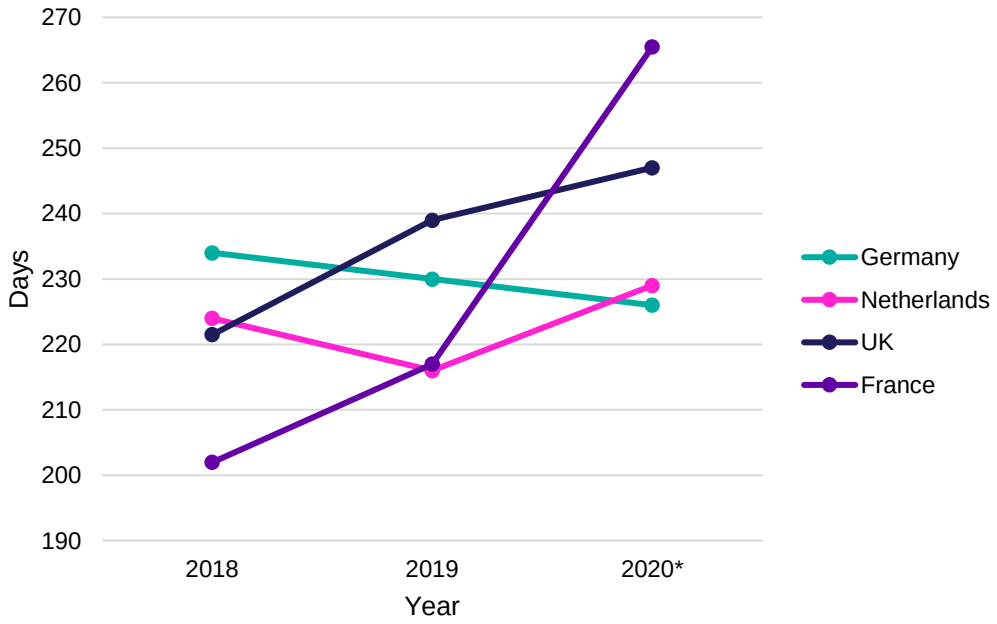
"I think where the Dutch can make a difference and where they have made a difference so far, is being open to having conversations outside of the system and not letting a system dictate what you can do." – ***Key player 6***

Source: Allucent, NCBI - Di Martino S, CCMO; N.B. Process chart is not exhaustive; Citeline primary research. Key players were interviewed for their insights, n=6

Timing from clinical trial application to first patient dosed

Out of Germany, Netherlands, UK, and France, the Netherlands had the fastest median time from clinical trial application to first patient dosed in 2019, and second fastest in 2020.

Median time from clinical trial application to a regulatory authority and the first patient receiving a first dose for a subset of commercial trials across all phases



* 2020 timings likely affected by COVID-19 pandemic

Number of trials included in the analysis of median time from clinical 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

Part of the fast clinical trial start-up timings for the Netherlands could be **competitive trial agreement execution timelines**:

3 out of 4 key player respondents are **satisfied** with clinical trial execution timings in the Netherlands

- Phase 1 trials in oncology in particular have optimized infrastructure for fast executions of CTAs (n=1 key player)
- However, speed is hospital-dependent – legal department often take a long time to review documents and hospital sub-departments give input to protocols they are not primarily involved in

Actions to reduce timelines in NL

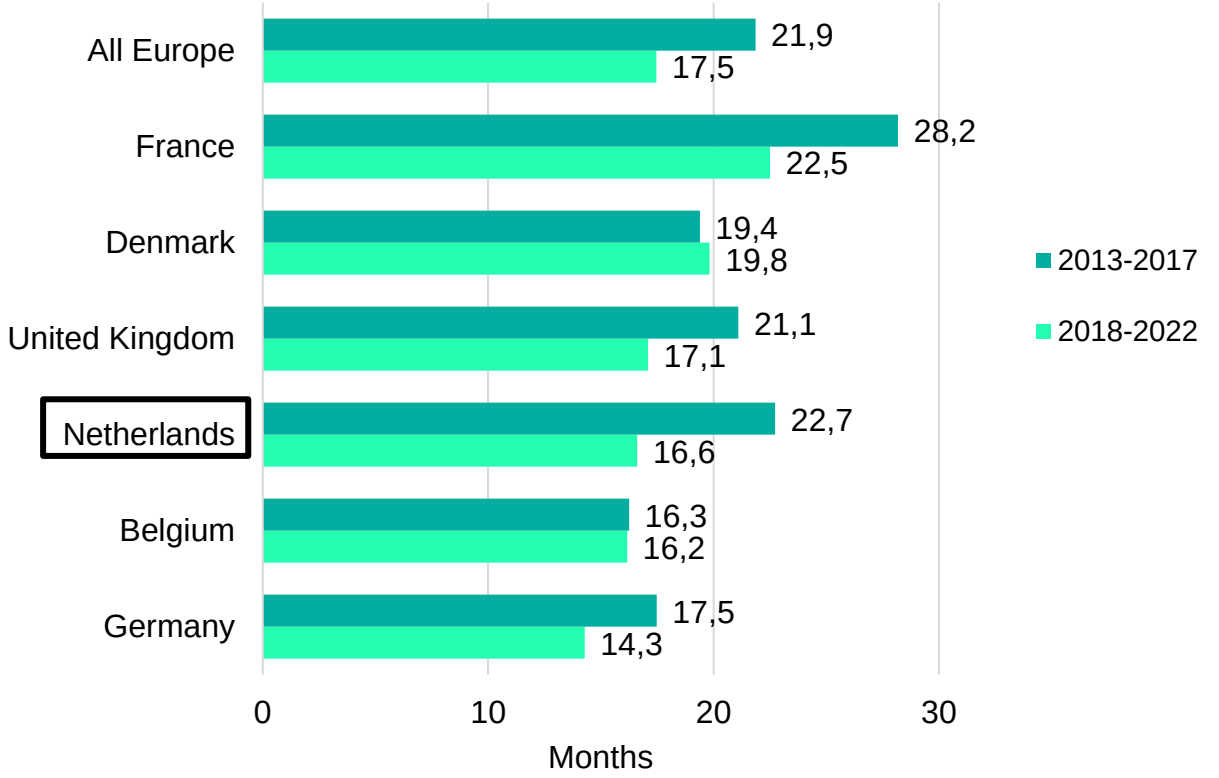
1. Introduce a central template which includes a section on trial-related costs
2. Increase the number of dedicated contract managers
3. Standardize the expected trial site cost of assessments on a national level

Source: UK Government Life Science Competitiveness Indicators 2022; Citeline Primary Research. Key players were interviewed for their insights, n=6

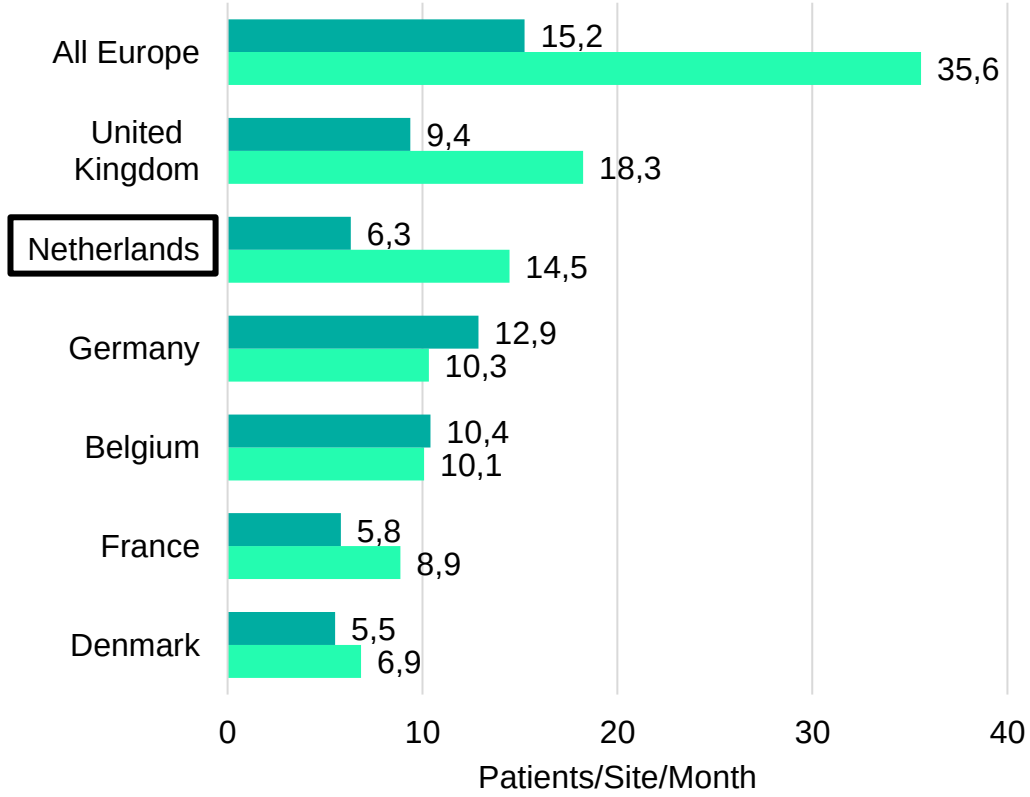
Enrolment duration time across all phases – single-country trials

Of 6 EU comparator countries, the Netherlands has the 4th shortest duration of enrolment and 2nd fastest enrolment rate when considering trials of all phases between 2018 and 2022

Average **time taken** to complete enrolment across all phases



Average **enrolment rate** across all phases

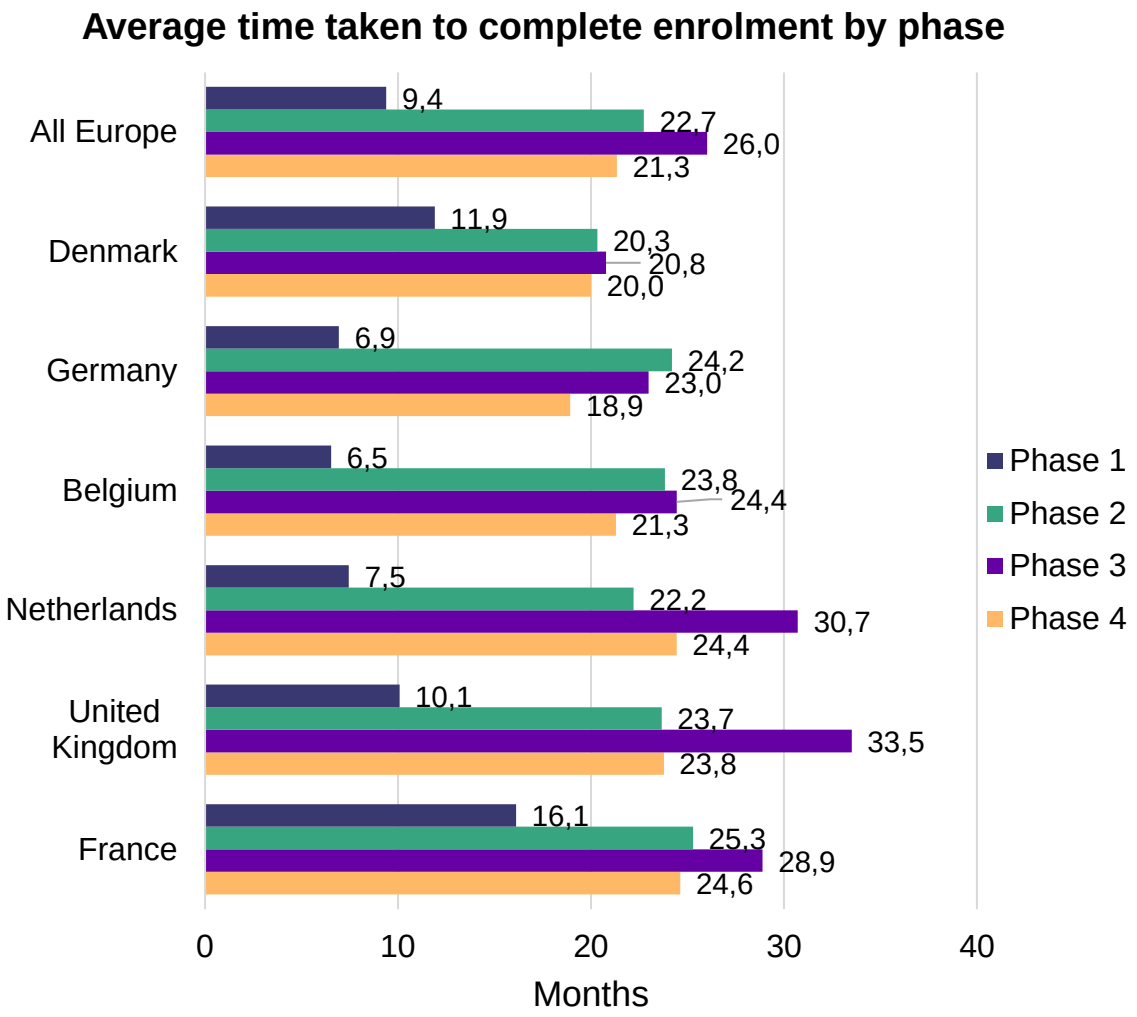


Enrolment duration for 2018-2022 trials in the Netherlands is shorter than the EU average

Sources: Citeline| Trialtrove

Phase segmented enrolment duration ranking – single-country trials

The Netherlands has the 3rd shortest duration of enrolment at Phase 1 and 2nd at Phase 2, but is the 2nd slowest at Phase 3 and 4



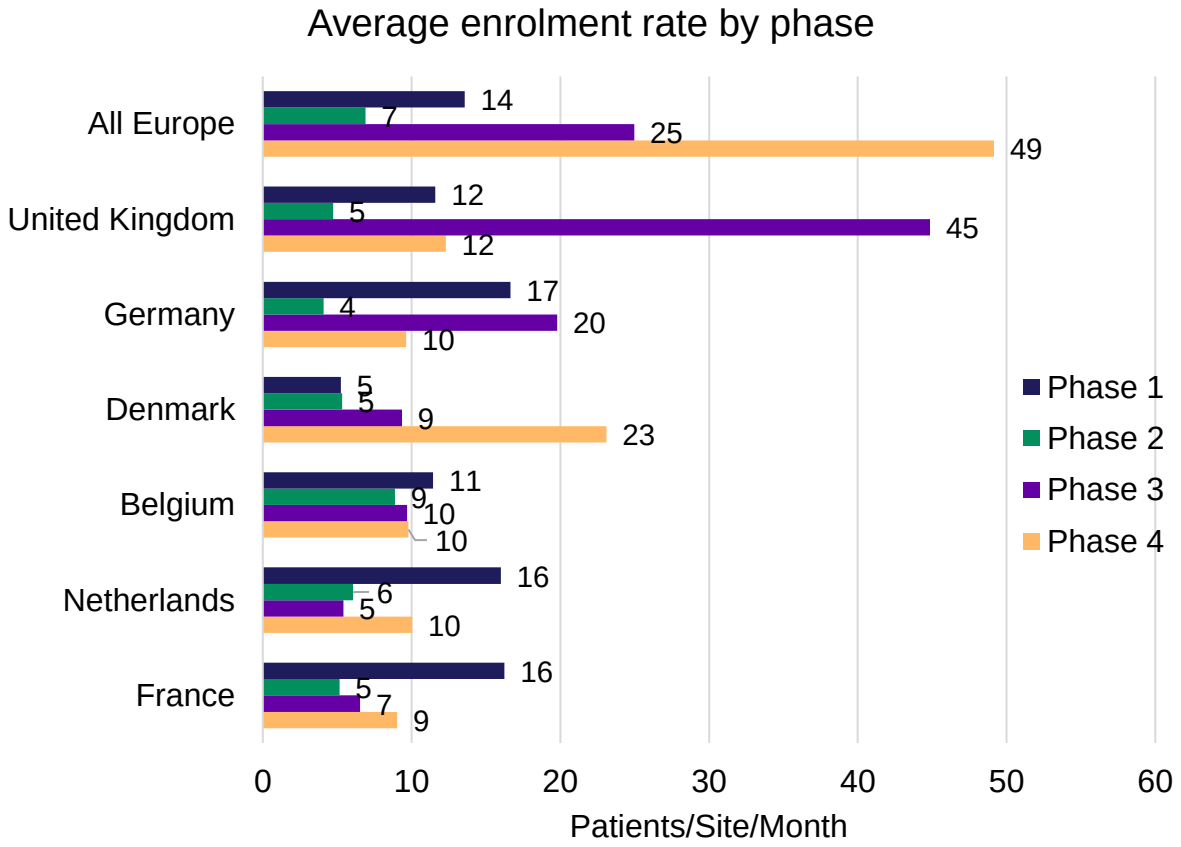
Rank (shortest to longest)	Phase 1	Phase 2	Phase 3	Phase 4
1	Belgium	Denmark	Denmark	Germany
2	Germany	Netherlands	Germany	Denmark
3	Netherlands	United Kingdom	Belgium	Belgium
4	United Kingdom	Belgium	France	United Kingdom
5	Denmark	Germany	Netherlands	Netherlands
6	France	France	United Kingdom	France

NB: Only single-country trials included in this analysis

Sources: Citeline| Trialtrove

Phase segmented enrolment rate ranking – single-country trials

Looking at enrolment rate, and therefore taking into account different patient enrolment targets, the speed of enrolment in the Netherlands is particularly fast for early-stage and Phase 4 trials



Rank (fastest to slowest)	Phase 1	Phase 2	Phase 3	Phase 4
1	Germany	Belgium	United Kingdom	Denmark
2	France	Netherlands	Germany	United Kingdom
3	Netherlands	Denmark	Belgium	Netherlands
4	United Kingdom	France	Denmark	Belgium
5	Belgium	United Kingdom	France	Germany
6	Denmark	Germany	Netherlands	France

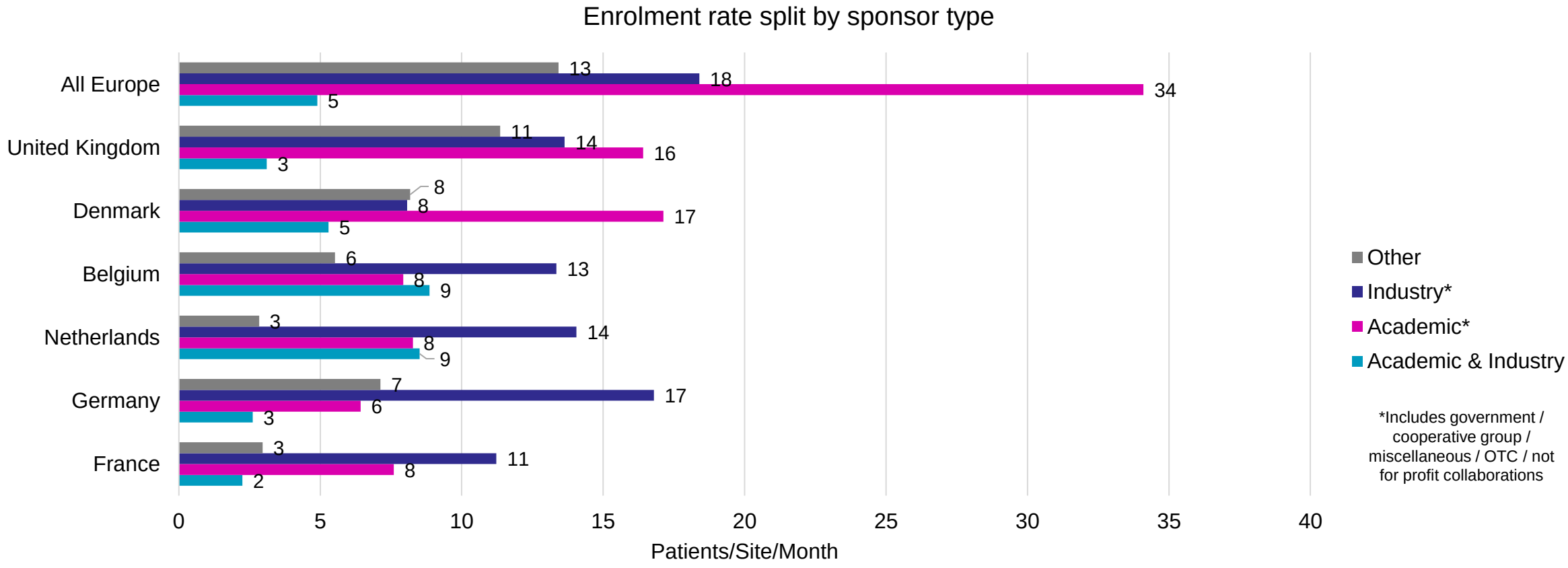
Note: U.K. phase 3 enrolment are particularly high due to COVID-19 trials with high patient volume & low site numbers

NB: Only single country trials included in this analysis

Sources: Citeline| Trialtrove

Enrolment rate by sponsor type – single-country trials

The enrolment rate for the Netherlands is fastest for industry-sponsored trials, having the joint 2nd fastest rate alongside the UK, behind Germany



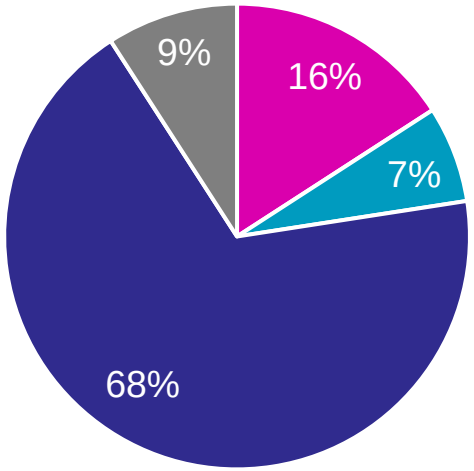
The Netherlands has the joint fastest enrolment rate for joint academic and industry trial, but is second slowest for academic studies alongside France and Belgium

Sources: Citeline| Trialtrove; Industry = any trial with an industry sponsor, but not academic; Academic = any trial with an academic sponsor but not industry; Academic & Industry = any trial with both an industry and academic sponsor; Other = any trial that has neither an industry nor academic sponsor

The proportion of different sponsor types

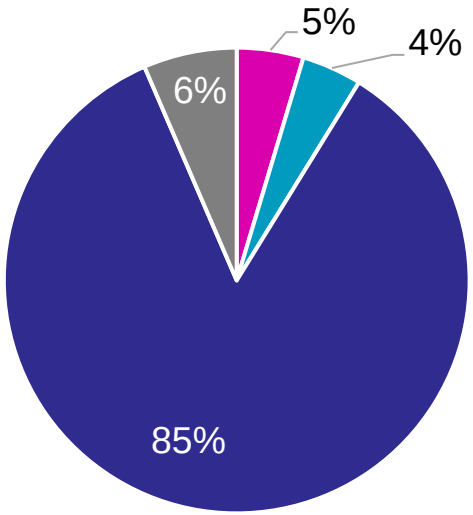
A far greater proportion of multinational trials with Dutch sites have an industry sponsor compared with Dutch single-country trials

Netherlands



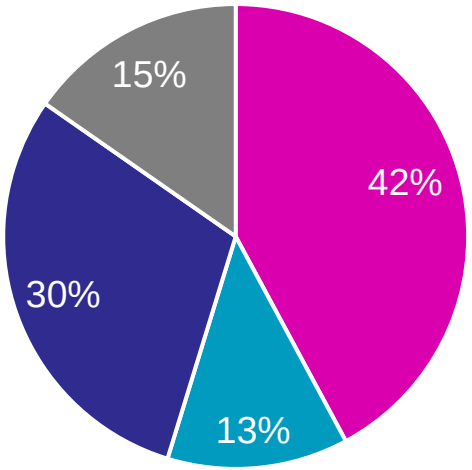
All trials

Netherlands



Multinational trials

Netherlands



Single-country trials

Academic* | Both Academic and Industry | Industry* | Other

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

The quick speed of enrolment for industry and joint industry-academic trials appears beneficial for multinational trials specifically, for which 89% of trials are sponsored either by both academic and industry groups collaboratively, or industry groups only

Sources: Citeline| Trialtrove; N.B: industry = any trial with an industry sponsor, but not academic; academic = any trial with an academic sponsor but not industry; both industry and academic = any trial with both an industry and academic sponsor; other = any trial that has neither an industry nor academic sponsor

Factors impacting recruitment into clinical trials: Netherlands

The Netherlands benefits from high population and hospital density and recruitment databases; limiting factors are trial awareness and mistrust of pharma

Assists enrolment

High population and hospital density →
- Particularly as the Netherlands is a relatively small country, this means **accessibility to trial recruitment centers is high**

Centre for Human Drug Research →
- Recruits patients and provides research facilities and patient accommodation for clinical trials
- Maintains a database of >50,000 active study participants and includes the **Ready-for-Research** which uses a pool of key pre-screened patient groups that are on standby for early-stage clinical trials

Strong collaboration and communication →
- Dutch stakeholders are responsive
- Smooth collaboration between stakeholders

"From a sponsor or CRO perspective, the Dutch are responsive, they're pragmatic, think in solutions and have a high standard with regard to quality." – ***Key player 1***

Hinders enrolment

Patient perspectives and awareness →
- Key players feel that more needs to be done to make patients aware of what trials are available to them
- Key players believe HCPs & patients are reluctant to work with them and have mistrust towards industry

"Accessibility of clinical research for oncology patients is good, but other outpatients need a standardized way to see where trials are being conducted and if they have access to it." – ***Key player 3***

"Many patient advocacy groups are still quite nervous of industry. It's a shame because increasingly patients are deciding themselves if they want to participate"– ***Key player 2***

Limited technology → There is a need for **more innovative tools** and **technology** to assist recruitment, including **models** that can help calculate realistic patient cohort sizes, and **use of data** on accrual from historic trials in the same study population

Recruitment competition → Issue of low population size is exacerbated when sites run too many competing studies

Source: Centre for Human Drug Research; GCP Mindset, Clinical Trials in the Netherlands and Belgium; Citeline Primary Research. KP = Key players. Key players were interviewed for their insights, n=6

Factors impacting recruitment into clinical trials: comparator countries

Many factors relevant to the Netherlands are applicable to other EU countries, though country-specific initiatives such as Denmark's "Trial Nation" do play a role

	Assists enrolment	Hinders enrolment
UK	▪ Research is mandated in the Health & Care Act to be considered as a core part of Healthcare Delivery	▪ Costing and contracting processes creates bottlenecks ▪ NHS suffers from staff burnout and record waiting lists, so capacity cannot meet clinical trial set-up demands within competitive timelines • Limited capacity is compounded by limited co-ordination between clinical trial sponsors and trial sites ▪ Despite the Health & Care Act mandate, research is often not considered to be a priority, undermining staff support and capacity for delivering clinical trials
France	▪ The country has a standard mandated template agreement for clinical trials ("Convention Unique"), for use by sponsors wishing to conduct trials in French hospitals	▪ Pharmaceutical companies and medical devices manufacturer clinical teams need to be trained on Convention Unique to make sure it is appropriately used
Germany	▪ High capacity - of the 6 EU countries, Germany has the greatest number of hospital beds per 100 people, and the greatest number of hospitals (the latter perhaps a virtue of being one of the geographically largest countries of the 6)	▪ Administrative burden – lack of sufficient, tailored software to facilitate recruitment, meaning a more manual/ labour-intensive process if currently used to find patients that match the recruitment criteria
Belgium	▪ At the end of 2017 the National Competent Authority (FAMHP) launched a campaign designed to encourage patients to enrol in clinical trials	▪ Due to the linguistic diversity across different regions in Belgium, all patient information needs to be translated into multiple languages (French, German, Flemish)
Denmark	▪ A free service (Trial Nation) for clinical trials in Denmark, makes study start-up more attractive as it can help with investigator identification, a co-ordinated feasibility process with a national response from hospital sites within 5 days, and access to established hospital and patient network partnerships	▪ A lack of communication between healthcare professionals and patients regarding the benefits of clinical trials

Source: ABPI: Recruiting patient access to industry clinical trials in the UK; Long-awaited update of the French "Convention Unique" for clinical trials finally published; Fitzer et al., JMIR Med Inform., 2022; Straube et al., Front. Oncol., 2017; pharma.be; Centre for Human Drug Research; Huiskens et al., Res Syn Meth, 2020; Ministry of Foreign Affairs of Denmark; Kjær et al., SN Comprehensive Clinical Medicine, 2019; Lyngsø et al., International Journal of Integrated Care, 2016; GCP Mindset, Clinical Trials in the Netherlands and Belgium

Ease of working with clinical trial stakeholders in the Netherlands

Stakeholders are easy to access and open to collaboration; however, areas for progress include improved patient opinion of industry, and ensuring scientific leaders do not remain too focussed on the Netherlands only

	Regulatory agencies	CROs and Manufacturers	Patient advocacy groups	Scientific leaders	Hospitals	Inter-country collaboration
Positive	▪ **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	▪ **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)
Areas for improvement	▪ Need **more frequent** communications ▪ **Improved alignment** between regulatory agencies and developers	▪ KP 1 mentioned that many CROs are **new to the Alzheimer's field** which can be challenging for that indication	▪ They can be **cautious of working with industry**, which could be difficult as patients become increasingly in charge of their own decisions to participate in clinical trials	▪ Need to ensure Dutch scientific leaders are **not making decisions** that are **too focussed** on the **Netherlands,** but instead **are taking into account** the **activity** of **scientific leaders** in the **broader EU**		▪ The Netherlands could improve inter-country collaboration by having dedicated CRAs for multinational trials and participating in international consensus meeting

*"With regulatory agencies, we have short communication timelines. Nonetheless, I wish we could communicate more often and align better"– **Key player 1***

*"Regarding patient advocacy groups or investigator consortiums, communication is not fantastic. Many patient advocacy groups are still quite nervous of industry. It's a shame because increasingly patients are deciding themselves if they want to participate"– **Key player 2***

*"…Sometimes scientific leaders deviate from what European colleagues are doing, putting us in an unpredictable situation. We should be careful we don't operate just on a country level, but that we acknowledge we are doing trials on a global level"– **Key player 3***

Comparison with wider EU

Of the key players that provided insight, key players 1, 2, and 6 felt that communication between clinical trial stakeholders in the Netherlands is **very similar to** in **other European countries**, while key players 5 felt it is easier in Netherlands

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

Accessibility of scientific advice in the Netherlands

There are multiple organisations that can provide advice and resource for clinical research, including groups at the regulatory level such as the CCMO and the MEB, and disease-specific foundations

National Competent Authority Scientific Advice

Details	▪ The Medicines Evaluation Board (MEB) provides scientific/regulatory advice relating to any stage of the product pipeline, to anyone from small research institutions to large pharmaceutical companies ▪ Anything related to medical ethics is under the remit of the Central Committee on Research Involving Human Subjects (CCMO) ▪ A procedure is also available for applicants to simultaneously request registration-related scientific advice from the MEB, and reimbursement advice from the Netherlands' National Health Care Institute
Transparency	▪ All data provided by companies/applicants in relation to the provision of advice is handled in the strictest confidence
Exemptions from frees	▪ A cheaper rate for scientific advice is available for small companies/start-ups and academic groups, primarily focussing on early stage development • The general rate for simple advice is 6,860 EUR, and for small companies/academics the rate for "customised advice" is 2,310 EUR

Member of ECRIN?: No

The European Clinical Research Infrastructure Network (ECRIN) works with national networks of clinical trial units and European correspondents to facilitate researchers in conducting multinational European clinical trials, focussing on investigator-sponsored clinical trials

Member of SNSA?: Yes

Scientific National Advice Service (SNSA) pilot, launched by the EU-Innovation Network is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously (i.e., from each member state in which they plan to conduct their trial) to enhance the quality and consistency of advice

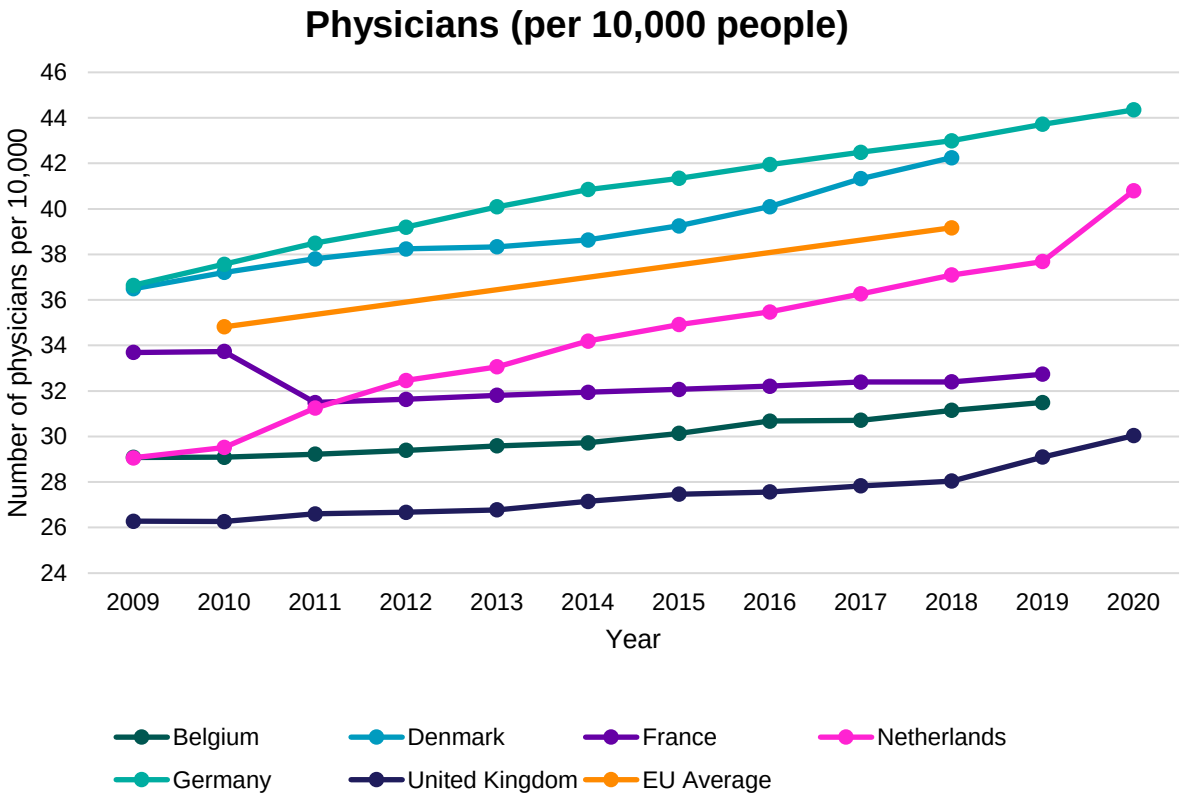
Other Organisations of note for Scientific Advice

Central Committee on Research Involving Human Subjects (CCMO)	▪ Designed to enact the Medical Research Involving Human Subjects Act, ensuring that research proposals are reviewed by an independent committee of experts
Dutch Clinical Research Foundation (DCRF)	▪ A group dedicated to increasing and ensuring the collaboration of individuals for clinical trials, including hospitals, researchers, patients, CROs, universities
National Institutes/Disease Foundations	▪ The Netherlands has multiple disease-specific foundations that can provide resources for clinical research e.g. HOVON (hemato-oncology foundation), the WCN (research network of cardiovascular institutes) and the Dutch MS Research Foundation

Sources: Medicines Evaluation Board; CCMO; HOVON; WNC; ECRIN; SNSA; Dutch MS Research Foundation; DCRF. For information on comparator country scientific advice, please see Appendix slides 90-94

Healthcare professionals per capita

Netherlands has had the third-highest number of physicians per capita since 2012, and had the highest growth in 2019-2020



Number of healthcare professionals in the Netherlands		
Speciality	**Number of physicians (2020)**	**Per 10,000 population**
Specialist medical practitioners	35,833	17.7
Generalist medical practitioners	31,037	9.1
General practitioners	15,931	8.6
Other generalist medical practitioners	15,106	20.4
General paediatricians	1,900	1.1
Gynaecologists and obstetricians	1,711	1.0

Number of practising nurses and midwives (2020)	Per 10,000 population
197,548	112.7

In the Netherlands, the number of medical doctors is regulated through caps on the number of medical students, at both a national and a university level. Medical schools are in private, nonprofit university medical centers.

Source: Eurostat, online data code HLTH_RS_SPEC, online data code: HLTH_RS_GRD, The Commonwealth Fund International Profiles of Health Care Systems (2020), World Bank

Clinical research networks in the Netherlands

There is a rich clinical research network landscape fragmented by speciality; oncology networks are divided by region but all aim to increase collaborative efforts and knowledge share

1964 – Dutch Society of Immunology
Aim to stimulate excellent immunological research and its application in clinical and laboratory diagnostics, and to promote the dissemination of knowledge about the immune system in disease and health

1988 – WCN (Werkgroep Cardiologische centra Nederland)
Cardiovascular investigators across 50+ institutions partnering with pharmaceutical companies, CROs and academic research organisations

2000 – Belgian Dutch Clinical Pathway Network (BDCPN)
Involved in over 1000 projects in 57 participating organisations across Belgium and the Netherlands

BDCPN supports multi-center research projects and international collaboration

2000 – The Vascular Research Network
Coordinate and execute the design of clinical studies between pharmacist, vascular internists, and cardiologists

2008 – Dutch Medicines for Children Research Network
All 8 university hospitals in the Netherlands, and 6 pharmaceutical companies assist in managing the local trial sites and facilitate recruitment in clinical trials

Its aim is to conduct and coordinate high-quality clinical drug trials in the pediatric population

2014 – ReSViNET - Respiratory Syncytial Virus Network
Specialty network that is focusing on RSV infections

Today there is a Dutch Patient Advisory Board consisting of 9 members and an International Patient Advisory Board

2015 – Regulatory Science Network Netherlands
A network of experts from industry, academia, government bodies, and the broader regulatory science field, with a mission of advancing the regulatory systems of medicines development, marketing authorization, and access

2016 – EMBRAZE
Oncology network in South-West Netherlands focused on joint clinical research

2017 – CONTRAST Consortium
A collaboration of academic researchers, private and public partners aiming to improve outcomes of stroke patients

2018 – Dutch Cardiovascular Alliance
Partners work together to mobilise a total of 1 billion euros for cardiovascular research and innovation

2019 – Oncomid
Oncology network with 13 expert teams across various hospitals in central Netherlands

2021 – OncoZon
Oncology network of 9 hospitals and 1 radiotherapy institute in the Southeast Netherlands region

Two OncoZON centers have been recognized as Centers of Excellence - MC Oncology Center and MUMC+ Comprehensive Cancer Center

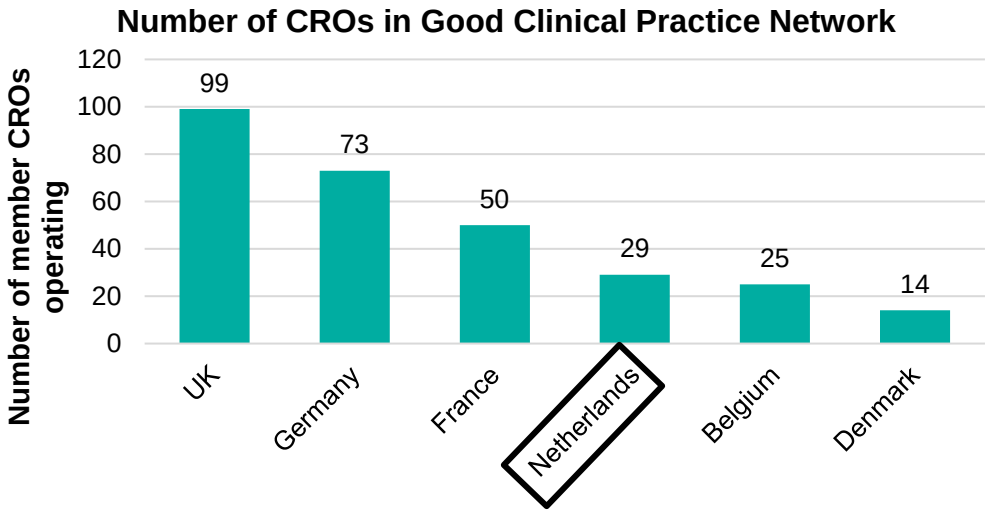
2023 – OncoNoVo+
Oncology network of all thirteen hospitals in the North Holland/Flevoland region

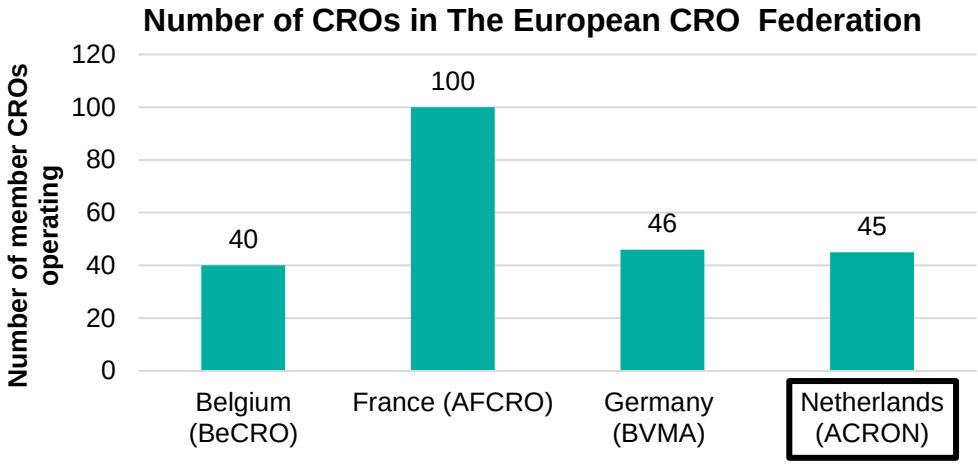
*"Within oncology you also see that there are certain diseases where we really excel compared to the others. In prostate cancer, bladder cancer and Phase I oncology those research networks are really well organised."– **Key player 3***

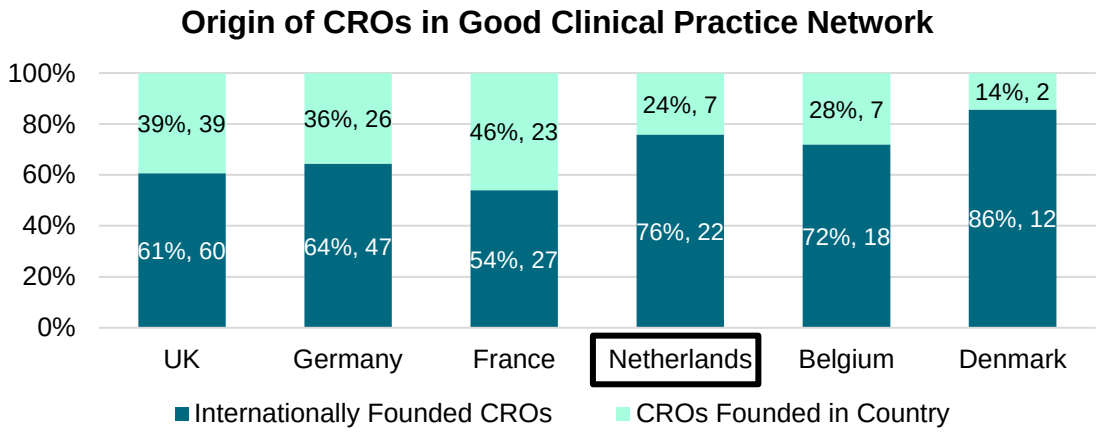
Source: NVVI-DSI; WCN Life; BDCPN; VRN; DMfCRN; resvinet; RSNN; Embraze; CONTRAST consortium; DCV alliance; Oncomid; OncoZon; Amsterdam UMC - OncoNoVo ;N.B. Not intended to be exhaustive; Citeline Primary ResearchKey players were interviewed for their insights, n=6. For details on comparator country research networks, please see Appendix slides 95-99

Contract research organisation networks

Of the 29 CROs in the GCP network operating in the Netherlands, only 7 (24%) are Dutch companies; ACRON, the Dutch node, represents 12% of EUCROF membership







- The Good Clinical Practice Network (GCP) list is now a paid subscription, and each contract research organisation (CRO) can be included upon request
- Dutch CROs belonging to the Good Clinical Practice CRO Network and operating within the Netherlands are: BioCult, Research Drive, Axon Medchem, Clinimetrics, Julius Clinical Research, Kinesis Pharma and SMS-Oncology
- 'Origin' is based on the country CRO was founded in or, if unavailable, then the country CRO is headquartered in
- The European CRO Federation (EUCROF), founded in October 2005, is comprised of 387 paying member CROs operating in 12 EU countries
  - In the Netherlands, the association of CRO is ACRON which consists of 45 companies and represents approximately 1200 employees in the CRO industry in the Netherlands
  - The ACRON members make up almost 12% of the EUCROF membership

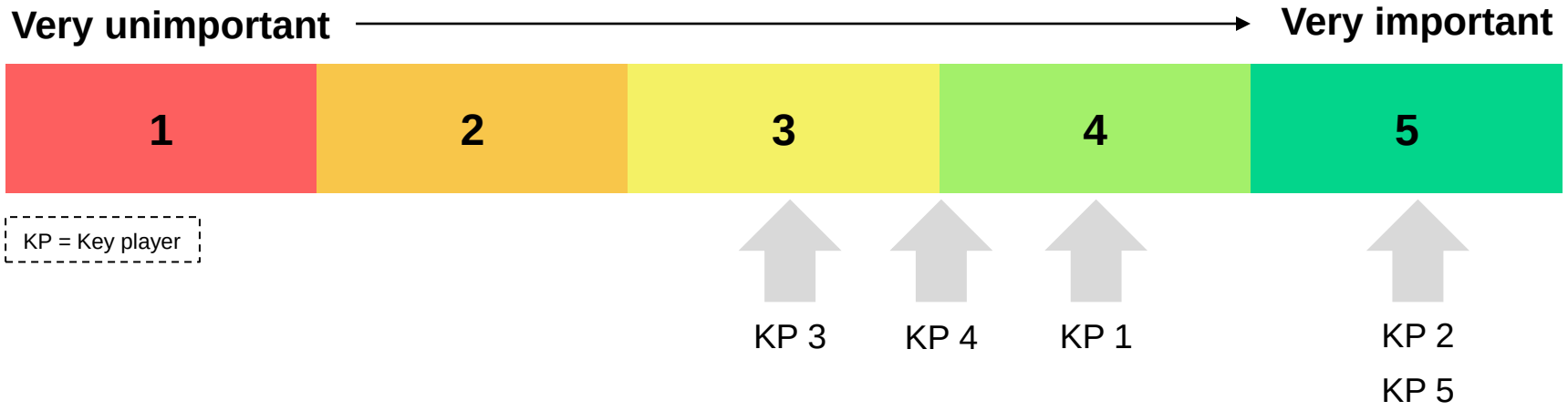
Source: Good Clinical Practice Network, European CRO Federation

Contract research organisation involvement and importance

Overall, key players deemed CROs to be of high importance in the Netherlands for reasons such as collaborative resourcing models, and their importance is of similar value in other EU countries

Importance of CROs in clinical trials in the Netherlands

Average = 4.1



Reasons for ranking

- **Collaborations** between organisations and CROs, particularly in functional service provision models, are prevalent in the Netherlands
  - Some organisations choose to keep everything in-house, while certain CROs have particular therapeutic area expertise
- **Integration and reduced dependence** on CROs are envisioned in the future if the Netherlands can implement chain integration , although they are currently considered necessary
- There is a **significant presence** of major CROs with offices in the Netherlands

Impression of CROs in other EU Countries

- The consensus was that the importance of CROs is similar across EU countries
- Key player 3 noted that different therapeutic area priorities across countries attract varied CROs

*"…we are collaborating with CROs more in terms of the functional sourcing-providing models. We reach out to them for us to provide a service in terms of providing us with the best CRAs and CTCs." – **Key player 3***

KP 6 did not have CRO expertise

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

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 I 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

Overview of ATMPs in the Netherlands

The Netherlands has been actively engaging in multiple cross-border collaborations to strengthen the ATMP landscape and also has established new ATMP Centres of Excellence

Overview:

- RegMed XB is a cross-border collaboration of ~500 Dutch and Belgian scientists at institutes in "Moonshots": long-term visions of breakthroughs for patients
  - There are currently four Moonshots: kidney, diabetes, osteoarthritis, and cardiovascular
- The MEB recommended the establishment of additional treatment centres for ATMPs, but given the complexity of the manufacturing process for ATMPs and the requirement for specialisation in ultra-orphan conditions, this is often not feasible
- The study of National Health Institute's (ZIN) live database of drugs in the lock, a cost-containment measure, showed that orphans are regularly placed in the system
  - Of the 21 products in the lock as of February 2022, 12 (57%) were orphans
  - This statistic disproportionately affects ATMPs

"Our medical expertise is very much advanced when you're talking about ATMP trials. I certainly think that Netherlands is an attractive country." – ***Key player 2***

2020 Kite Pharma's CAR-T manufacturing facility in Hoofddorp became fully operational

Oct 2021 The Netherlands, Austria, Belgium, Ireland and Luxembourg have, as part of the BeNeLuxA, negotiated a pricing agreement with Novartis over its gene therapy Zolgensma for treating spinal muscular atrophy

Jun 2022 Researchers from LUMC successfully used stem cell gene therapy to treat a baby with the severe congenital immune disorder

Oct 2022 Skåne University Hospital, Lund University in Sweden and Leiden University Medical Center announce international collaboration to develop research, education and care delivery in ATMPs

Apr 2023 BeNeLuxA jointly agreed to end the negotiation discussions on reimbursement with Orchard Therapeutics Limited regarding Libmeldy, a gene therapy for metachromatic leukodystrophy

2020

2021

2022

2023

2020 NecstGen is founded to support the ATMP ecosystem
It is a non-profit spin out of LUMC located in Leiden Bio Science Park and funded by RegMed XB

2022 A central Core Facility was established in the Erasmus MC to facilitate ATMP development and effectively translate these promising products to our clinics and patients.

Dec 2022 NecstGen received its GMP Manufacturing License for ATMPs

Feb 2023 The Netherlands-HQ company uniQure announced European Commission approval of Hemgenix, the first gene therapy for adults with haemophilia B

Source: 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, Abbreviations: ZIN - Zorginstituutnederland / National Health Institute; Press release, Kite Pharma, June 2020, link; Press release, uniQure, Feb 2023, link

Ranking by number of ATMP trials

The Netherlands is ranked 3rd for number of ATMP trials among European comparator countries when trial numbers are adjusted to account for differing population sizes

	ATMP (cell and gene therapies)	
Ranking	**Overall number of trials**	**Adjusted for population size (per 10,000)**
1	UK (155 trials)	Belgium (0.07 trials)
2	Germany (137 trials)	Denmark (0.05 trials)
3	France (128 trials)	Netherlands (0.05 trials)
4	Netherlands (86 trials)	UK (0.02 trials)
5	Belgium (66 trials)	France (0.02 trials)
6	Denmark (29 trials)	Germany (0.02 trials)

Attractiveness

All key players felt that the Netherlands is an attractive environment for ATMP trials due to:

- Logistical coordination
- Advanced research and medical expertise
- Authorities being open to discussions and innovation

"I think we are attractive because we are able to run these trials and to administer these innovative drugs." – ***Key player 1***

"Yes, I think very attractive because, logistically, it's very well coordinated in the Netherlands." – ***Key player 5***

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

Challenges to ATMP Access and Clinical Trials, Netherlands

Areas for improvement include creation of dedicated infrastructure and removing barriers to access once products have reached the market

Assessment

- Very difficult for ATMPs placed in lock (sluis list*) to satisfy The National Health Care Institute criteria for a positive recommendation
  - The sluis restricts reimbursement until certain criteria are fulfilled which can take up to 9 months
- The criteria for inclusion in the lock are problematic for ATMPs

Affordability

- Joint procurement via BeNeLuxA, a joint assessment initiative, is possible, but variation in approach to assessment and procurement may delay/prevent access
- It is unclear what flexibility exists around Institute for Clinical and Economic Review (ICER) thresholds for ATMPs for rare diseases

Availability

- Involvement in joint negotiations may delay access in some situations
- Willingness to use cross border initiatives is unknown

Accessibility

- Variable acceptance of single treatment centres – they are not preferred by the MEB in the Netherlands due to the risk of a single-point failure

Trials

Key players from the Dutch clinical trial landscape identified the following barriers for ATMP trials:

- **Shortage of personnel**
  - Particularly specialised nurses who can conduct ATMP trials
  - Resourcing for manufacturing
- **Lack of dedicated infrastructure**
  - The current infrastructure is not tailored for ATMPs, leading to bottlenecks and inefficiencies
  - Only academic hospitals have the necessary accreditation to conduct ATMP studies, limiting the number of available sites
- **Collaboration challenges**
  - Collaboration can be hindered by existing work progress among departments and organisations involved in ATMP trials

Impact of the challenge on access from highest (full Harvey ball) to lowest (an empty, white Harvey ball)

*All innovative drugs are put in ‘the sluis’ if budget impact > € 20 million or cost per use of patient are higher than € 50,000 and the total per year amounts to € 10 million or more

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

Proposed solutions and feasibility to ATMP challenges, Netherlands

Promoting the Netherlands' expertise in ATMP research could improve the trial landscape, and leveraging and strengthening involvement in BeNeLuxA is central to improving access to ATMPs once approved

Assessment of feasibility of solutions to be implemented: + low feasibility, ++ medium feasibility, +++ high feasibility

Assessment

- Reform of the assessment criteria for ATMPs in lock **++**
- Raise the lock cost threshold for ATMPs and spread cost over duration of treatment benefit **++**

Affordability

- Improve early dialogue with all parties in BeNeLuxA process to align on assessment approach **+++**
- Flexibility around ICER thresholds needs to be made explicit for ATMPs in rare diseases **++**

Availability

- Continued dialogue with BeNeLuxA stakeholders in order to better prepare for future engagements **++**
- Increased collaboration on treatment centre optimisation within BeNeLuxA or other cross-border initiatives **+**

Accessibility

- Engage with treatment centres for coordination with network hospitals (clinical / ERN) **+**

Trials

Key players from the Dutch clinical trial landscape have identified the following proposed solutions to ATMP trial barriers:

- Build a **dedicated infrastructure** for ATMP research, including recruiting specialized personnel
- **Comply** with delivery **timelines**, especially First-Patient-In
- Focus more on the **site mapping** as opposed to country-level mapping
- **Promote expertise** in ATMP research through participation in panels, conferences, and strategic advertising
- Create a **more uniform environment** across academic hospitals

"Recruit more dedicated people (CPMs [Clinical Project Managers], contract managers, research nurses) in the Netherlands to strengthen the infrastructure." ***– Key player 5***

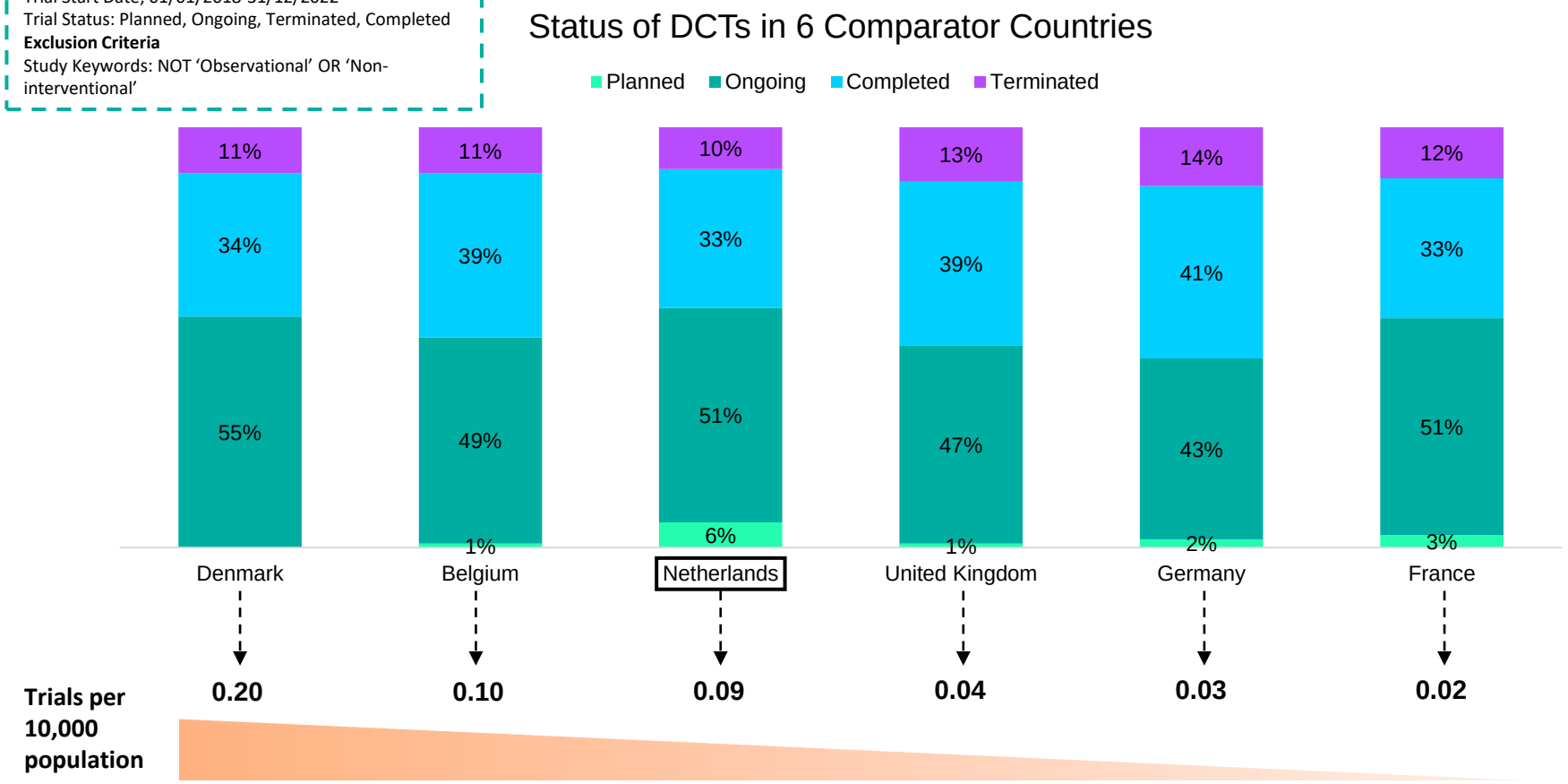
"Yes, we do map the countries which have the best chance of finding patients and little competition, but for ATMPs it's the name of the hospital that matters most." ***– Key player 2***

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

Decentralised clinical trials status, 2018-2022

Although the Netherlands' high proportion of planned decentralized trials indicates growing interest, key players have expressed skepticism of the extent to which this design will be adopted

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 players were doubtful of the future of decentralised trials in the Netherlands

- **Fully decentralized trial adoption** is **unlikely**, but **aspects** such as wearables and local blood draws are seen as potential elements that **could be utilized**
- The **Netherlands** is **small** and has a **good** travel **network**; therefore, patients and specialists (especially oncologists) **prefer on-site** visits
- The **push** for **decentralization** is likely to come **from sponsors** and **CROs**
- One key player believed the Netherlands would follow whatever trend is being seen seen worldwide
- One key player believes the Netherlands' small size makes it ideal to pilot decentralization, and that the country are open to innovation

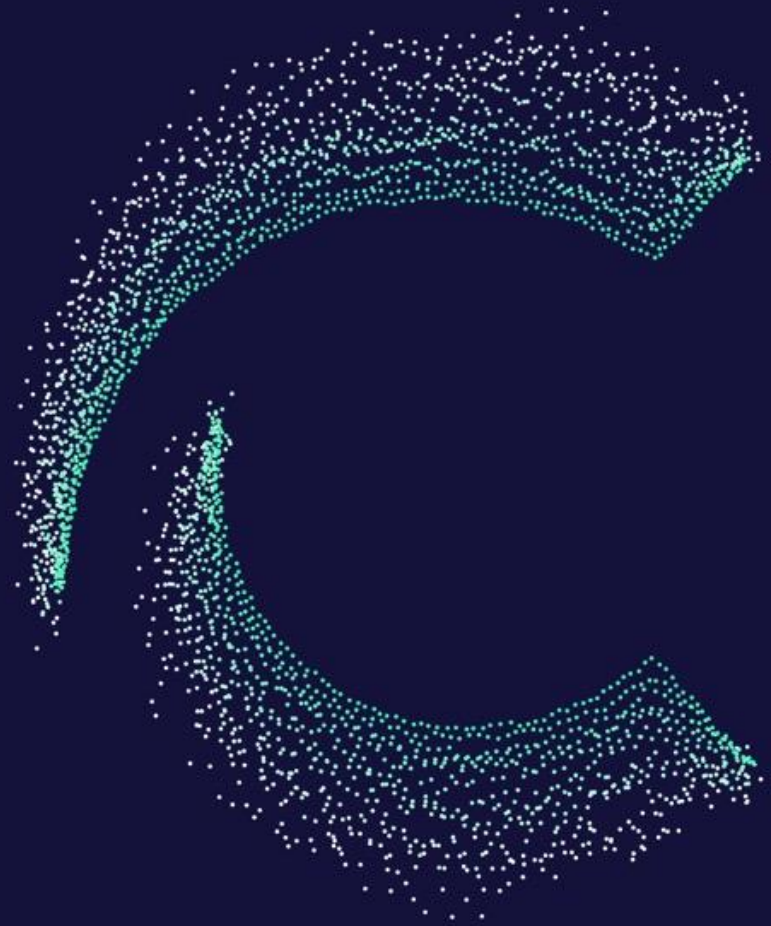
"Fully decentralised? No. Especially oncologists, they want to see their patients, they want to look them in the eye." ***– Key player 1***

Source: Citeline|Trialtrove; Clinical Trials Arena - DCT 2022 review; Clinical Trials Arena - DCT adoption tracker; Clinical Trials Arena - DCT factors; Citeline Primary Research. Key players were interviewed for their insights, n=6

CITELINE

Factors Impacting Site Selection

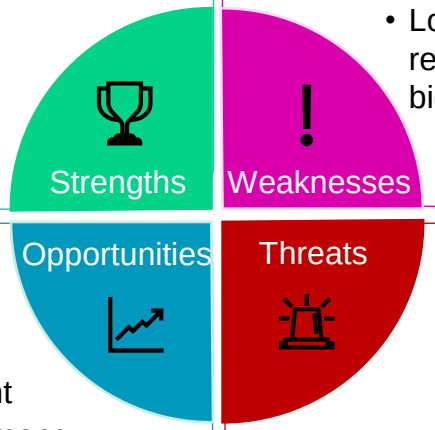
4.3 Availability of patients



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

SWOT analysis – availability of patients

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



Strengths

- The Netherlands has the shortest enrolment duration for phase 1 & Phase 4 industry sponsored trials, and the fastest enrolment rate for phase 1 academic sponsored trials*
- 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

Weaknesses

- Poor implementation of national electronic health record system vs competitors (e.g., Belgium eHealth platform)
- Perceived low public awareness of clinical trials
  - KOLs felt that further education is needed for the Dutch population on clinical trials
- Low population size limits the number of patients who can be reached and creates competition for the same patient population (a bigger problem for higher patient count trials)
  - Demonstrated through slow academic sponsored trial enrolment rates and durations at phase 4

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
- Technology is well leveraged in the Netherlands to facilitate ease of access to patients

Threats

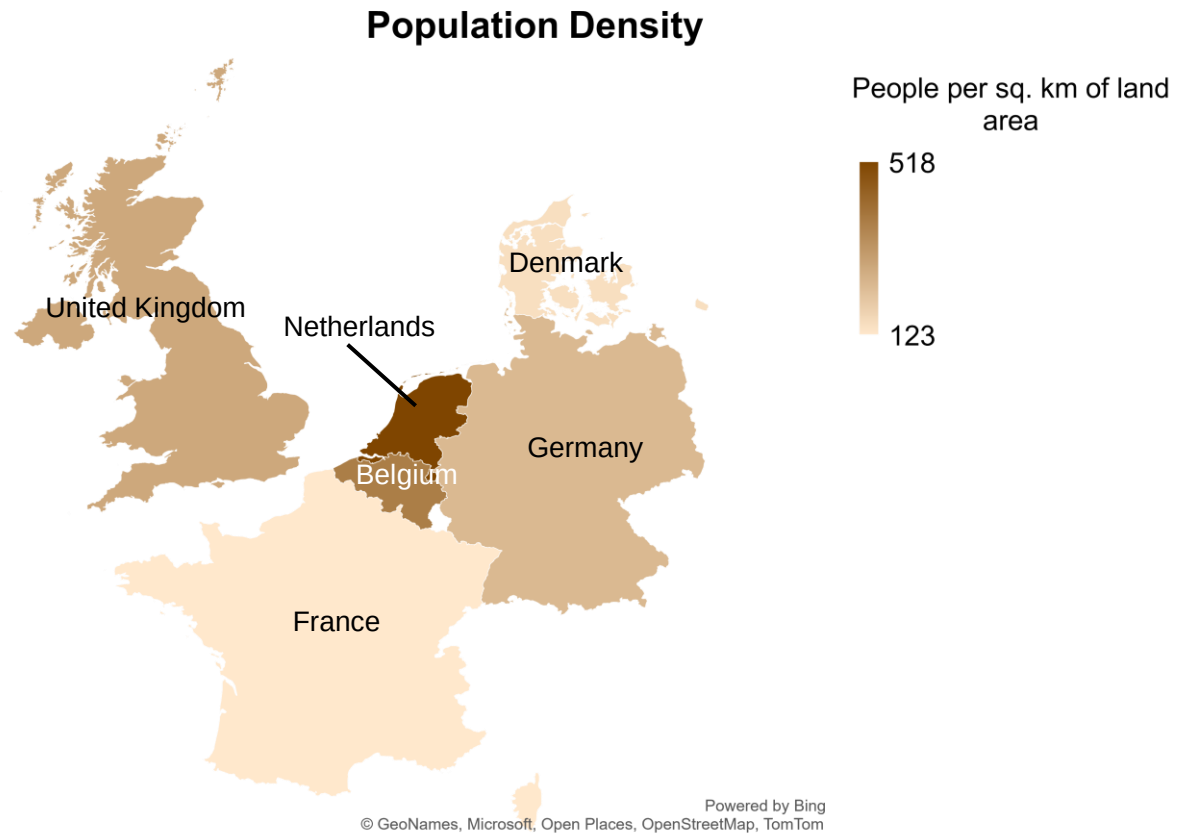
- Competition for limited patient pools at intra and inter hospital level
  - Limits the count of trials that can be efficiently enrolled
- Challenger attitude from patients towards pharma makes industry trials harder to recruit

*Single-country trials initiated between 2018-22; COVID-19 trials removed

Sources: Citeline| Trialtrove; Citeline Primary Research; Belgium eHealth Platform.

Population density

The Netherlands has the highest population density in comparison to the surrounding comparator countries, and over 4 times the density of all EU countries on average; this density improves access to patients



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 they have the disease and 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"– ***Key player 2***

Source: The World Bank - Population Density; The World Bank - Population Total; Citeline Primary Research. Key players were interviewed for their insights, n=6

Enrolment rate ranking

The Netherlands has demonstrable resilience in the face of unforeseen enrolment challenges and is historically well positioned for recruiting phase 1 trials

	Enrolment rate (Patients/Site/Month)		
Country	**2013-2017**	**2018-2022** ↓	**Enrolment resilience**
European Average	15.2	15.9	↑
Germany	12.9	9.4	↓
France	5.8	7.9	↑
United Kingdom	9.4	7.3	↓
Belgium	10.4	7.2	↓
Netherlands	**6.3**	**6.4**	↑
Denmark	5.5	6.2	↑

Enrolment resilience during COVID-19 pandemic

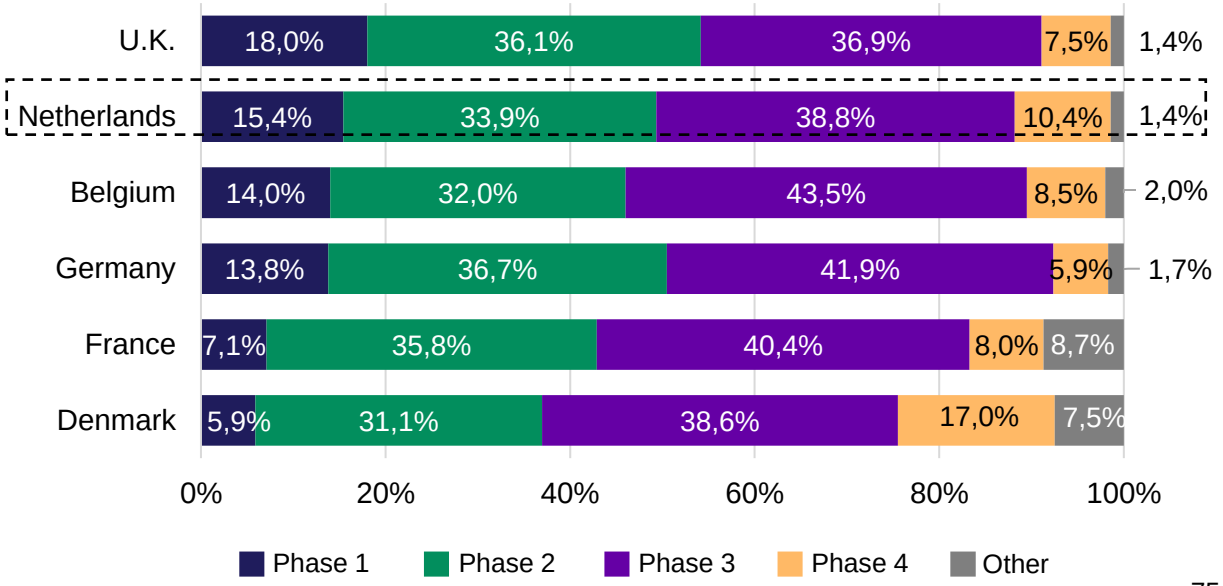
This analysis examine the **average enrolment rate regardless of phase, therapeutic area (excluding COVID-19) or sponsor type**

- The restrictions imposed by the COVID-19 pandemic placed pressures on the ability of many countries to recruit patients and caused some enrolment rates to flounder
- The Netherlands has demonstrated an ability to resist these unexpected challenges despite its smaller population size
  - The Netherlands was one of just three countries in the comparison group that were able to increase the enrolment rate of their non-COVID 19 related clinical studies during the years 2018-2022

Early phase trial specialism

- The Netherlands' small population size can pose difficulties in recruitment for later phase trials as these require a larger number of patients
  - The country is better suited for recruiting to phase 1 studies with reduced patient requirements
  - The Netherlands ranks 2nd place among the 7 comparator countries, behind the UK, for the proportion of phase 1 trials initiated between 2018-2022 (15.4%)

Trials by phase 2018-2022



Source: Citeline| Trialtrove

Industry sponsored trials – enrolment duration

The Netherlands has the shortest enrolment durations for phase 1 & 4 industry-sponsored trials (single-country trials 2018-2022); however, long enrolment times in phase 2 gives the country an overall ranking of 4th

	Phase 1		Phase 2		Phase 3		Phase 4		Overall	
Ranking (Shortest to longest)	Country	Average Months	Country	Average Months	Country	Average Months	Country	Average Months	Country	Average Months
1	Netherlands	5.84	Belgium	9.21	Denmark	8.74	Netherlands	7.81	Belgium	8.06
2	France	6.21	Denmark	9.53	Netherlands	9.61	United Kingdom	10.45	United Kingdom	8.39
3	Belgium	6.22	United Kingdom	12.46	Germany	14.66	Germany	12.40	Denmark	8.42
4	Denmark	6.27	Germany	18.64	France	16.65	Denmark	12.98	Netherlands	8.83
5	Germany	6.87	France	20.18	United Kingdom	26.94	France	17.47	Germany	9.20
6	United Kingdom	7.16	Netherlands	20.31	Belgium	32.98	Belgium	34.17	France	16.33

NB: Industry sponsors only (includes collaborations with government / cooperative group / miscellaneous / OTC / not for profit groups); Only single-country trials included in this analysis; COVID-19 trials removed

Sources: Citeline| Trialtrove

Industry sponsored trials – enrolment rate

The Netherlands is consistently ranked in the mid-table for enrolment rate for industry-sponsored trials (single-country trials 2018-2022), ranking overall 3rd out of 6

	Phase 1		Phase 2		Phase 3		Phase 4		Overall	
Ranking (Fastest to slowest)	Country	Average Patients/ site/Mo	Country	Average Patients/ site/Mo	Country	Average Patients/ site/Mo	Country	Average Patients/ site/Mo	Country	Average Patients/ site/Mo
1	Germany	14.22	Denmark	10.37	Denmark	20.15	United Kingdom	52.38	Germany	12.60
2	France	12.55	United Kingdom	7.33	France	9.51	Germany	23.82	United Kingdom	10.60
3	Netherlands	10.72	Belgium	7.12	Germany	5.35	Netherlands	13	Netherlands	9.03
4	United Kingdom	9.64	France	2.99	Netherlands	4.24	France	10.20	Denmark	8.84
5	Belgium	8.85	Netherlands	2.56	United Kingdom	3.05	Denmark	5.78	Belgium	8.24
6	Denmark	3.39	Germany	2.13	Belgium	0.79	Belgium	0.52	France	7.27

NB: Industry sponsors only (includes collaborations with government / cooperative group / miscellaneous / OTC / not for profit groups); Only single-country trials included in this analysis; COVID-19 trials removed

Sources: Citeline| Trialtrove

Academic sponsored trials – enrolment duration

The Netherlands has short phase 1 & 2 enrolment duration times in academic-sponsored trials (single-country trials 2018-2022); the country ranks 2nd overall despite comparatively longer times in phase 3 & 4

	Phase 1		Phase 2		Phase 3		Phase 4		Overall	
Ranking (Shortest to longest)	Country	Average Months	Country	Average Months	Country	Average Months	Country	Average Months	Country	Average Months
1	Denmark	7.77	Netherlands	20.11	Belgium	23.54	Germany	20.58	Denmark	21.60
2	Netherlands	14.52	Denmark	22.33	Germany	24.01	Denmark	21.52	Netherlands	22.29
3	Germany	14.76	United Kingdom	24.79	Denmark	26.34	United Kingdom	22.62	Germany	23.81
4	United Kingdom	22.95	France	26.86	Netherlands	27.02	Belgium	22.88	Belgium	24.51
5	Belgium	24.60	Germany	27.65	France	28.57	Netherlands	23.32	United Kingdom	25.43
6	France	29.35	Belgium	33.02	United Kingdom	32.69	France	25.40	France	26.98

NB: Academic sponsors only (includes collaborations with government / cooperative group / miscellaneous / OTC / not for profit groups); Only single country trials included in this analysis; COVID-19 trials removed

Sources: Citeline| Trialtrove

Academic sponsored trials – enrolment rate

The Netherlands has the fastest phase 1 enrolment rate for academic-sponsored trials (single-country trials 2018-2022); ranks 5th place overall due to fast enrolment rates in later phases from the comparator countries

	Phase 1		Phase 2		Phase 3		Phase 4		Overall	
Ranking (Fastest to slowest)	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**
1	Netherlands	5.45	Germany	7.96	Belgium	12.79	France	13.97	France	9.42
2	United Kingdom	4.37	France	7.25	Denmark	10.09	Denmark	7.06	Denmark	6.30
3	Denmark	2.53	Netherlands	6.07	France	7.32	United Kingdom	5.31	Germany	5.72
4	Germany	2.01	Denmark	3.8	Netherlands	4.26	Belgium	5.04	Belgium	5.26
5	Belgium	1.66	United Kingdom	2.59	Germany	3.13	Netherlands	4.89	Netherlands	5.19
6	France	1.07	Belgium	1.93	United Kingdom	2.99	Germany	4.82	United Kingdom	3.83

NB: Academic sponsors only (includes collaborations with government / cooperative group / miscellaneous / OTC / not for profit groups); Only single country trials included in this analysis; COVID-19 trials removed

Sources: Citeline| Trialtrove

Academic & industry sponsored – enrolment duration

When sponsored by both academic & industry sponsors, trials in the Netherlands have relatively average enrolment durations with the exception of phase 2 (single-country trials 2018-2022)

	Phase 1		Phase 2		Phase 3		Phase 4		Overall	
Ranking (Shortest to longest)	Country	Average Months	Country	Average Months	Country	Average Months	Country	Average Months	Country	Average Months
1	Belgium	5.26	Netherlands	17.47	Denmark	18.92	United Kingdom	15.62	Belgium	17.40
2	Germany	7.84	France	18.93	Germany	21.97	Belgium	19.37	Denmark	20.34
3	Denmark	12.64	Denmark	21.53	Belgium	26.06	Denmark	20.69	Netherlands	21.91
4	Netherlands	20.16	Belgium	24.31	Netherlands	30.77	Germany	20.87	Germany	22.86
5	United Kingdom	21.04	Germany	24.84	United Kingdom	32.01	Netherlands	23.12	United Kingdom	23.18
6	France	29.29	United Kingdom	25.96	France	35.42	France	26.11	France	24.42

NB: trials with at least one academic AND industry sponsors (includes collaborations with government / cooperative group / miscellaneous / OTC / not for profit groups); Only single country trials included in this analysis; COVID-19 trials removed

Sources: Citeline| Trialtrove

Academic & industry sponsored – enrolment rate

The Netherlands is the second-fastest enroller of phase 2 trials sponsored by both academic & industry sponsors (single-country trials 2018-2022)

	Phase 1		Phase 2		Phase 3		Phase 4		Overall	
Ranking (Fastest to slowest)	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**	**Country**	**Average Patients/ site/Mo**
1	Belgium	17.43	Belgium	21.31	Belgium	3.19	United Kingdom	15.58	Belgium	11.26
2	Denmark	16.38	Netherlands	4.10	Germany	3.07	Netherlands	5.43	United Kingdom	5.51
3	Germany	4.26	France	3.51	France	2.72	Belgium	3.62	Netherlands	4.36
4	United Kingdom	4.06	Denmark	3.47	Netherlands	2.10	Denmark	2.88	Denmark	4.22
5	Netherlands	3.25	United Kingdom	1.87	United Kingdom	2.08	France	2.86	France	3.07
6	France	1.48	Germany	1.80	Denmark	0.42	Germany	1.80	Germany	2.06

NB: trials with at least one academic AND industry sponsors (includes collaborations with government / cooperative group / miscellaneous / OTC / not for profit groups); Only single country trials included in this analysis; COVID-19 trials removed

Sources: Citeline| Trialtrove

CITELINE

Patients count in single-country trials across therapy areas and per capita

The Netherlands leads in patients treated per 100,000 of the population in Oncology trials at 13.9; it is also competitive in CNS trials at 2nd most per 100,000 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

*"For paediatric oncology in the Netherlands, eight academic hospitals have merged into one huge paediatric oncology centre. That's the Princess Maxima Medical Centre in Utrecht. It is the biggest centre in Western Europe" – **Key player 3***

Highest patient count per 100,000 population

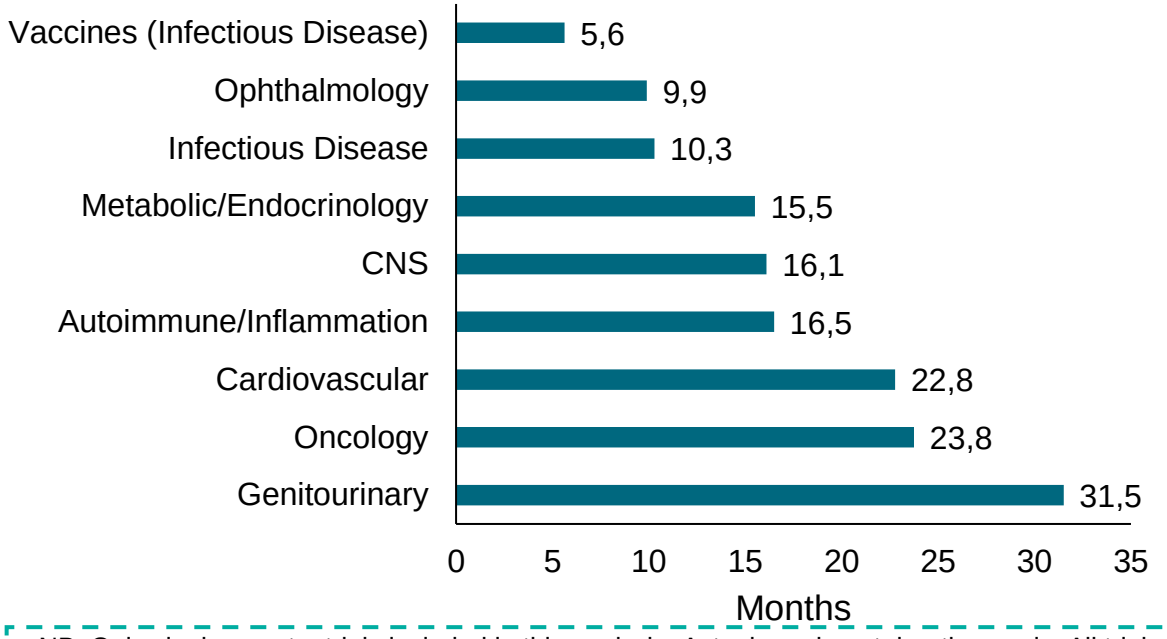
*A single Phase 4 Measles trial is responsible for the high count of patients in Denmark-based Vaccine trials.These analyses are for single-country trials only; These analyses include COVID-related trials; These analyses assess actual patient accrual counts

Sources: Citeline| Trialtrove

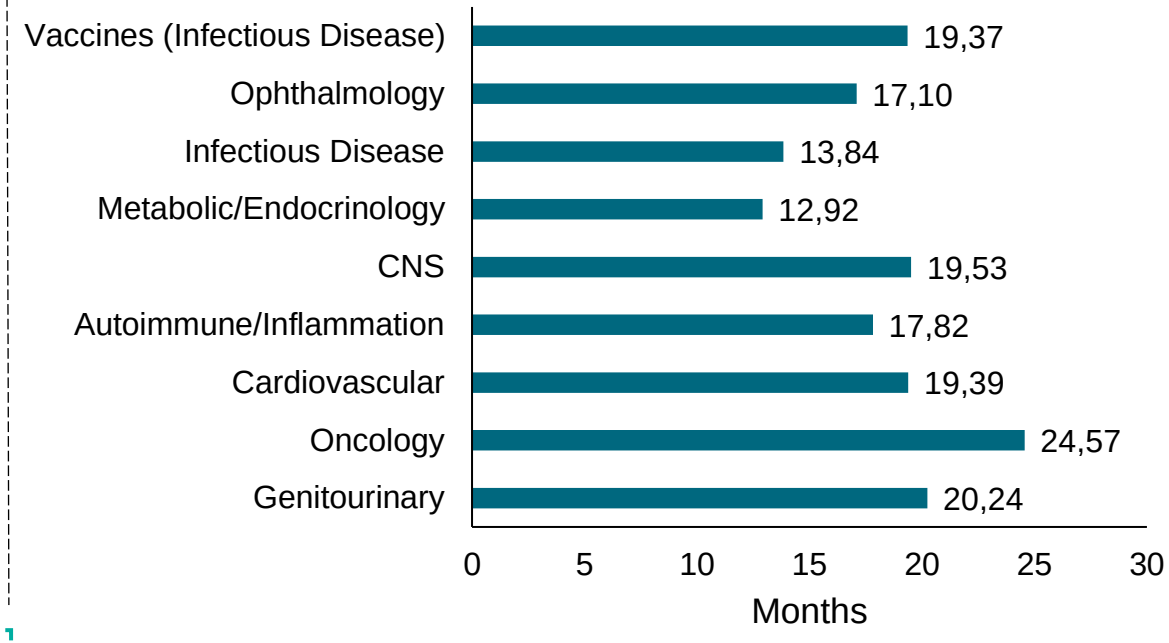
Enrolment duration by TA – Netherlands vs 6 comparator countries

The Netherlands has particularly short enrolment durations for vaccine, ophthalmology & infectious disease trials – however, there is large variation between countries

Netherlands enrolment duration



6 comparator countries enrolment duration



NB: Only single-country trials included in this analysis; Actual enrolment durations only; All trial phases included; trial start dates 2018-2022; No COVID-19 trials are included in the analysis

Key player views on Dutch TA specialisms

*"For oncology there are a lot of patient associations. The hospital makes sure that you are introduced to one of these patient associations or websites. Some of these websites contain an overview of all clinical trials and which are looking for patients"– **Key player 4***

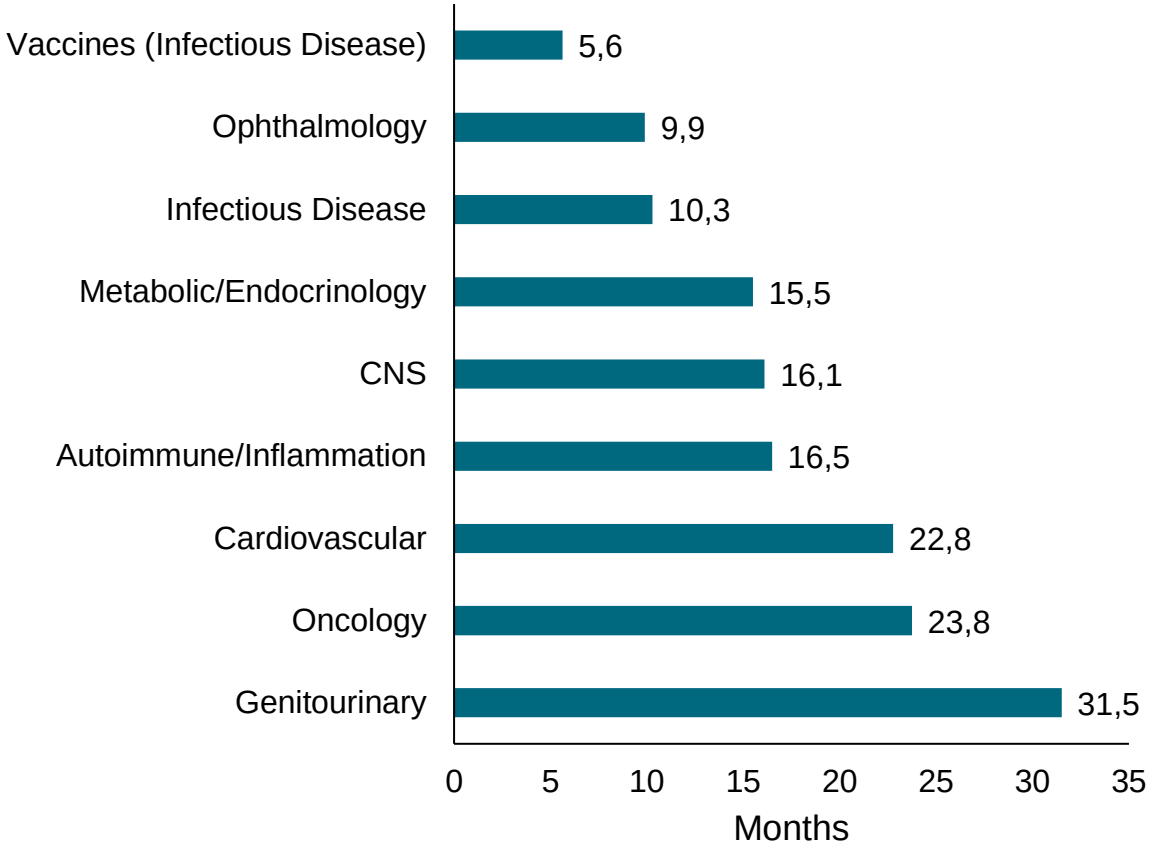
*"For Cardiovascular KOL networks the Dutch are ahead of other countries. There are fantastic networks in place called the WCN and the VRN"– **Key player 3***

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

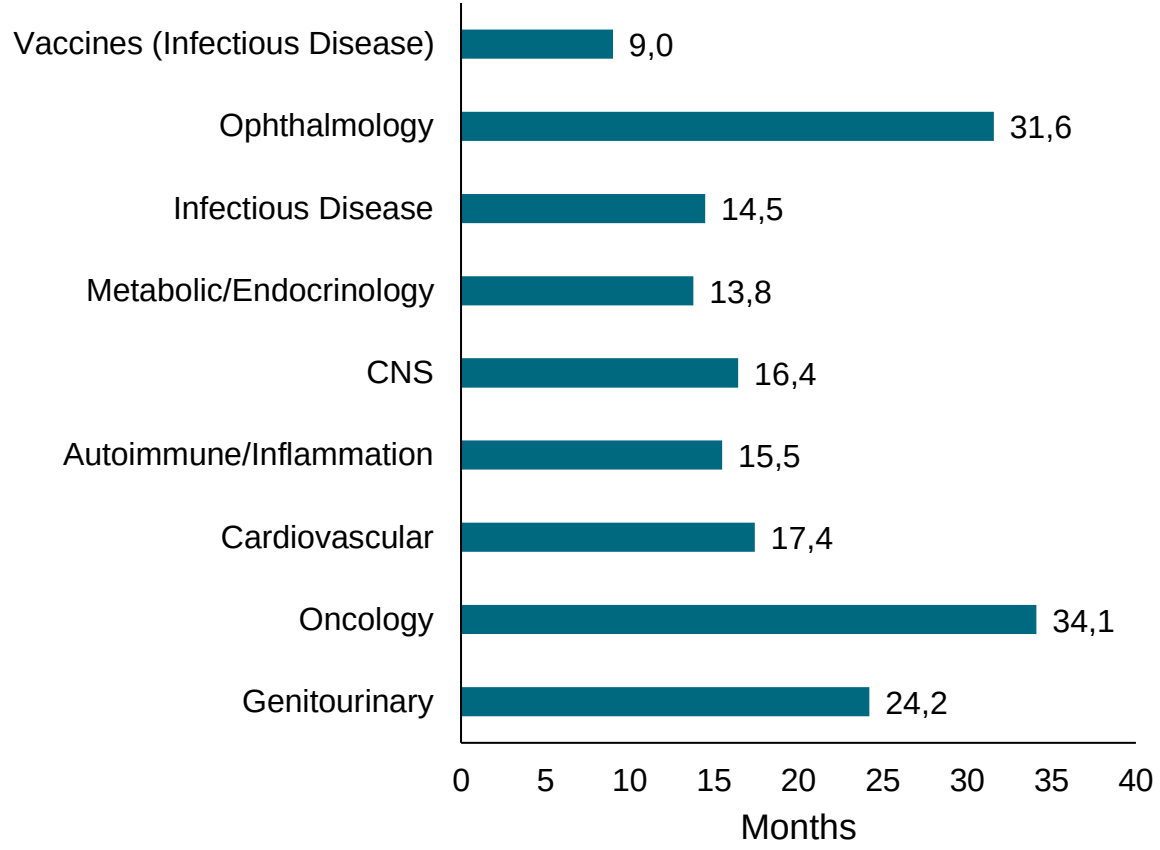
Enrolment duration by TA – Netherlands vs Belgium

The Netherlands is slower than Belgium to complete enrolment of cardiovascular trials, but this constitutes a higher proportion of trials in NL (10% vs 7%). NL enrols ophthalmology and oncology in a much shorter time

Netherlands enrolment duration



Belgium enrolment duration



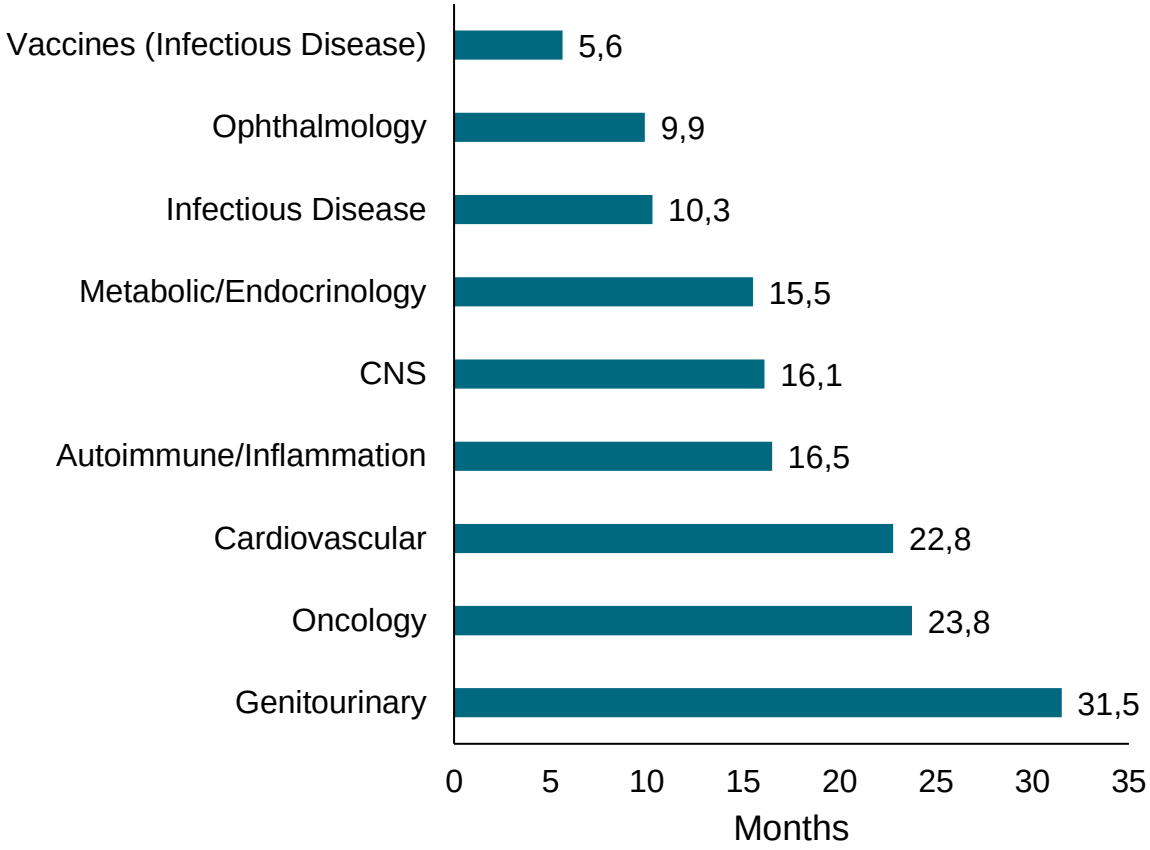
NB: Only single-country trials included in this analysis; Actual enrolment durations only; All trial phases included; trial start dates 2018-2022; No COVID-19 trials are included in the analysis

Sources: Citeline| Trialtrove; NB: Only single-country trials included in this analysis

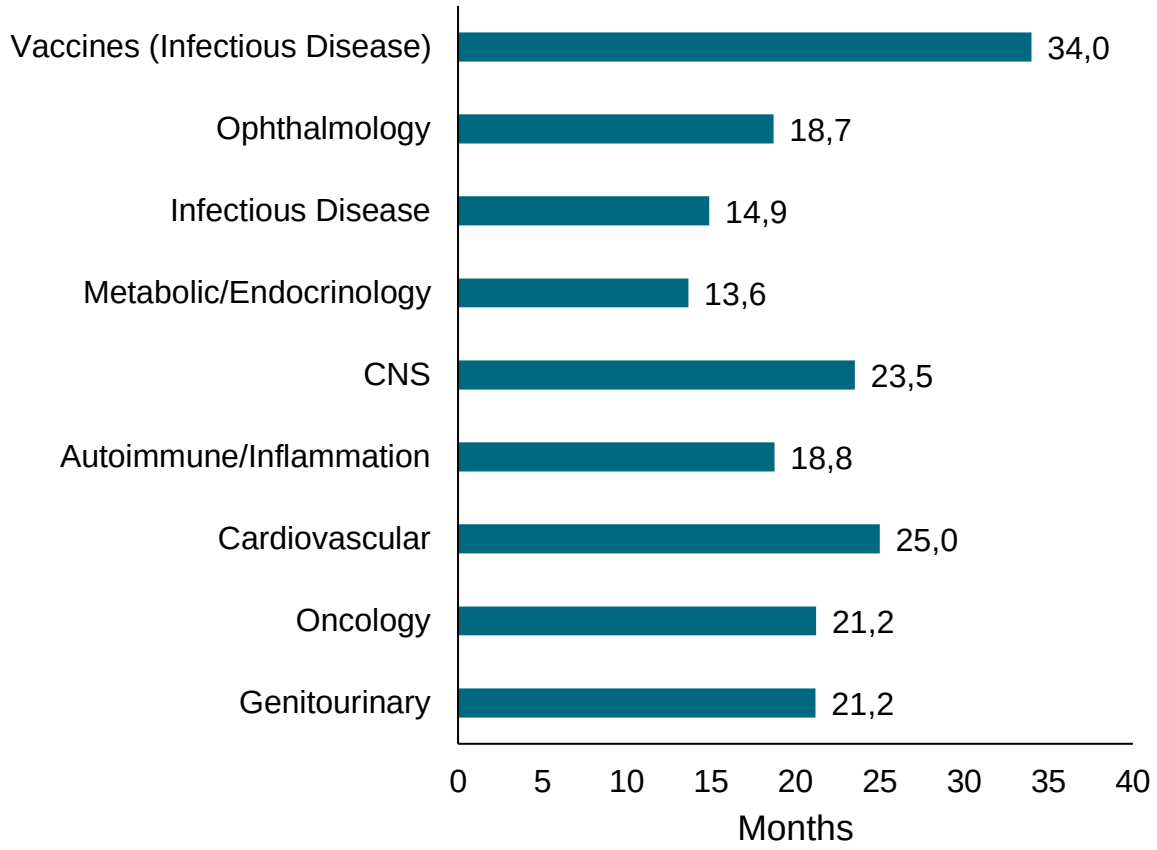
Enrolment duration by TA – Netherlands vs Denmark

Denmark has a 6x longer enrolment duration for vaccine trials than NL despite this TA accounting for 2% of trials in both countries; Denmark is faster for metabolic/endocrinology, oncology & genitourinary trials

Netherlands enrolment duration



Denmark enrolment duration



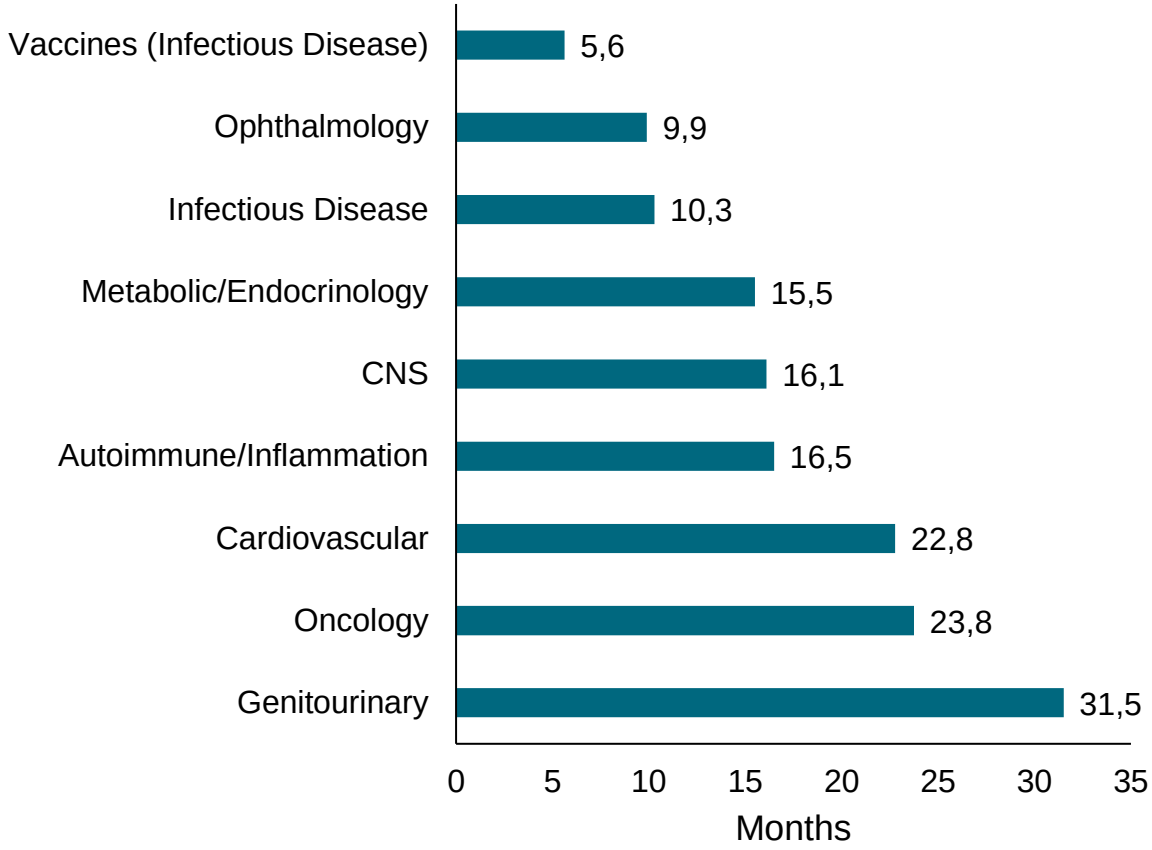
NB: Only single-country trials included in this analysis; Actual enrolment durations only; All trial phases included; trial start dates 2018-2022; No COVID-19 trials are included in the analysis

Sources: Citeline| Trialtrove; NB: Only single-country trials included in this analysis

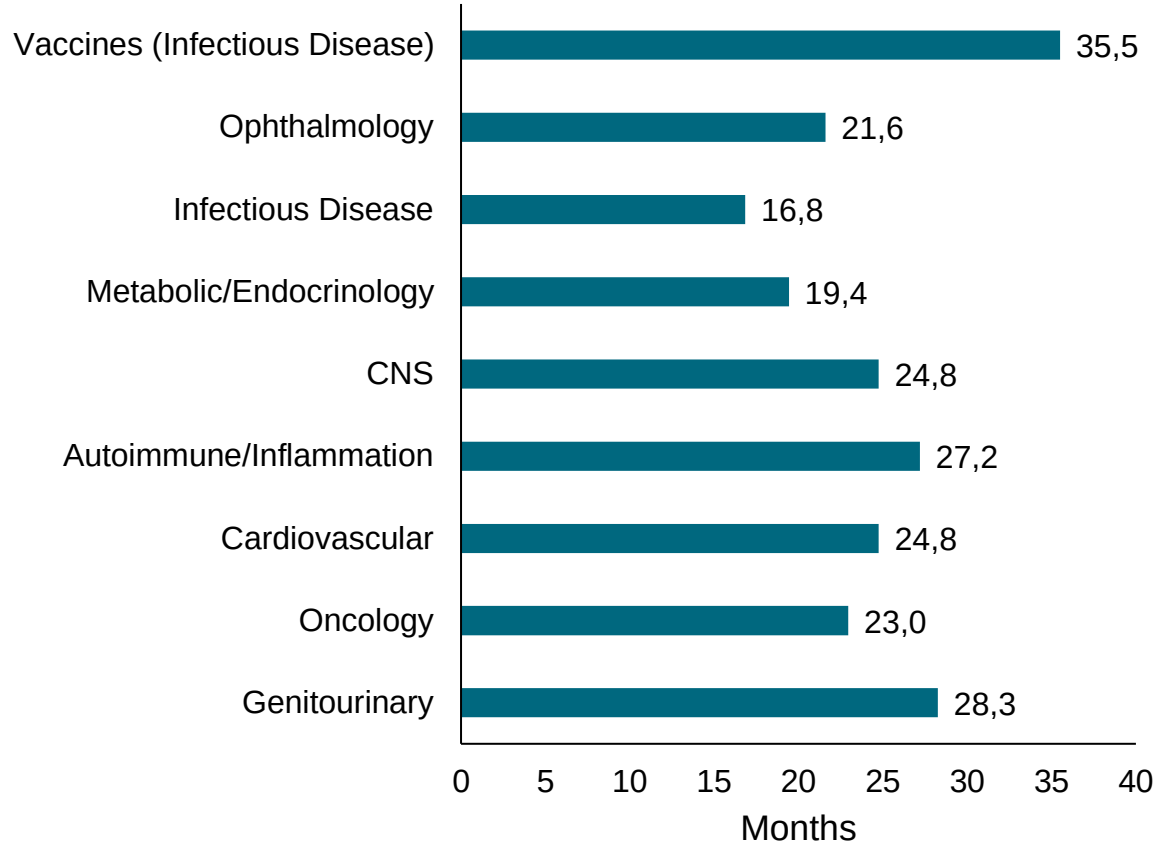
Enrolment duration by TA – Netherlands vs France

The Netherlands has shorter enrolment durations than France in the majority of assessed TAs, the only exceptions being oncology and genitourinary

Netherlands enrolment duration



France enrolment duration



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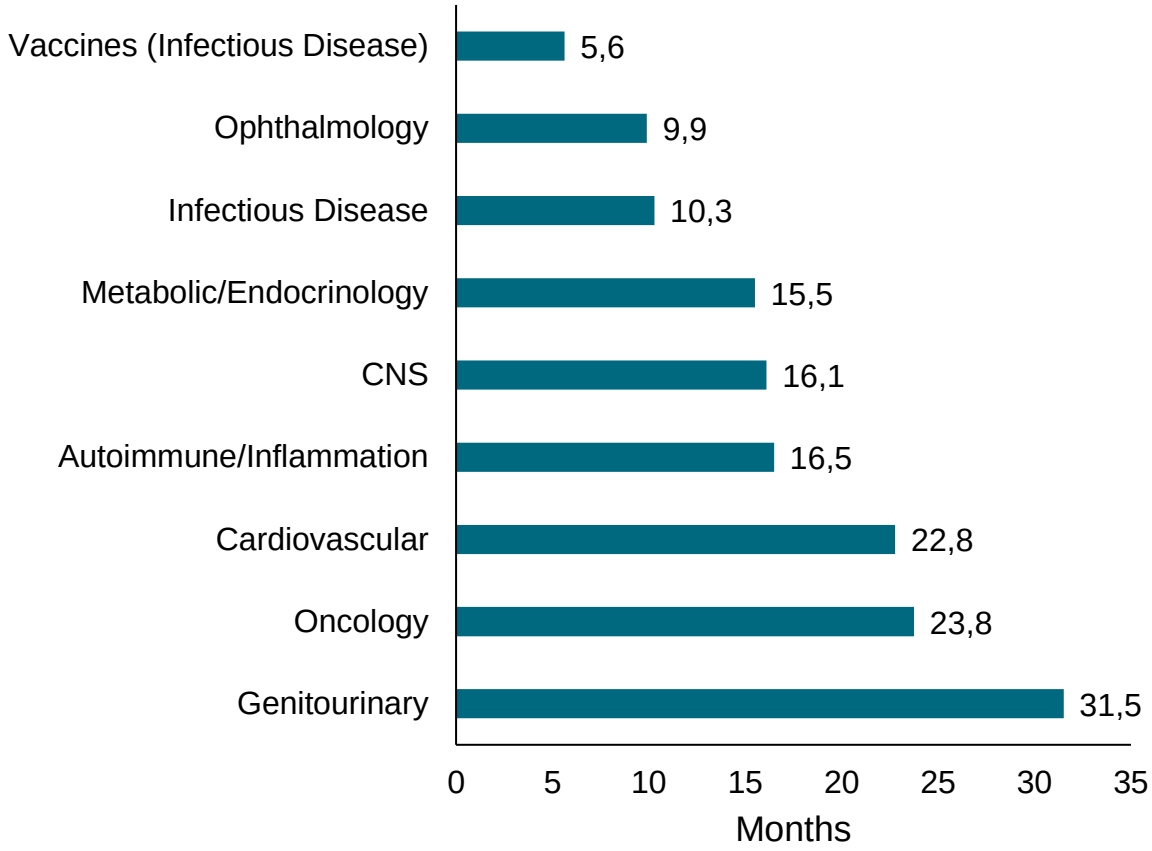
Sources: Citeline| Trialtrove; NB: Only single-country trials included in this analysis

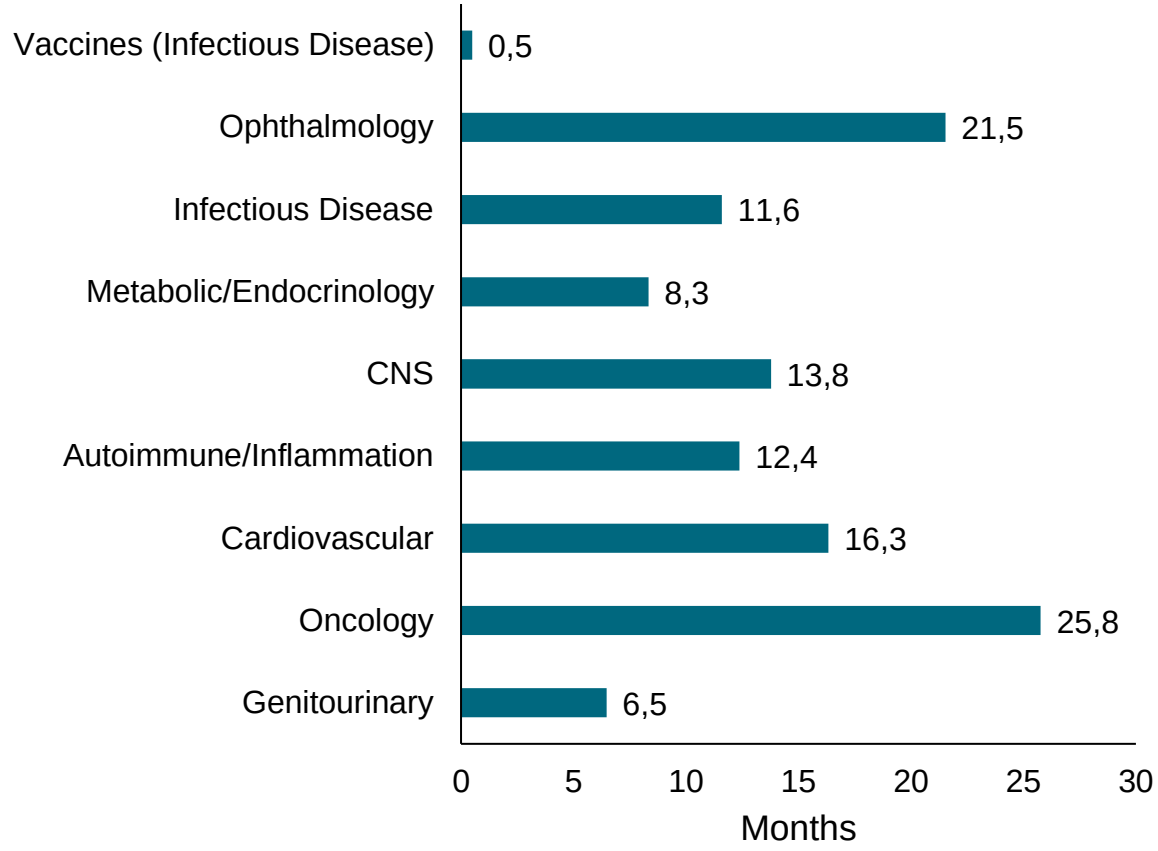
Enrolment duration by TA – Netherlands vs Germany

Vaccine enrolment duration for Germany is particularly fast but this represents a single trial with a low patient count (21); NL stands out from Germany in ophthalmology, infectious disease and oncology

Netherlands enrolment duration



Germany enrolment duration



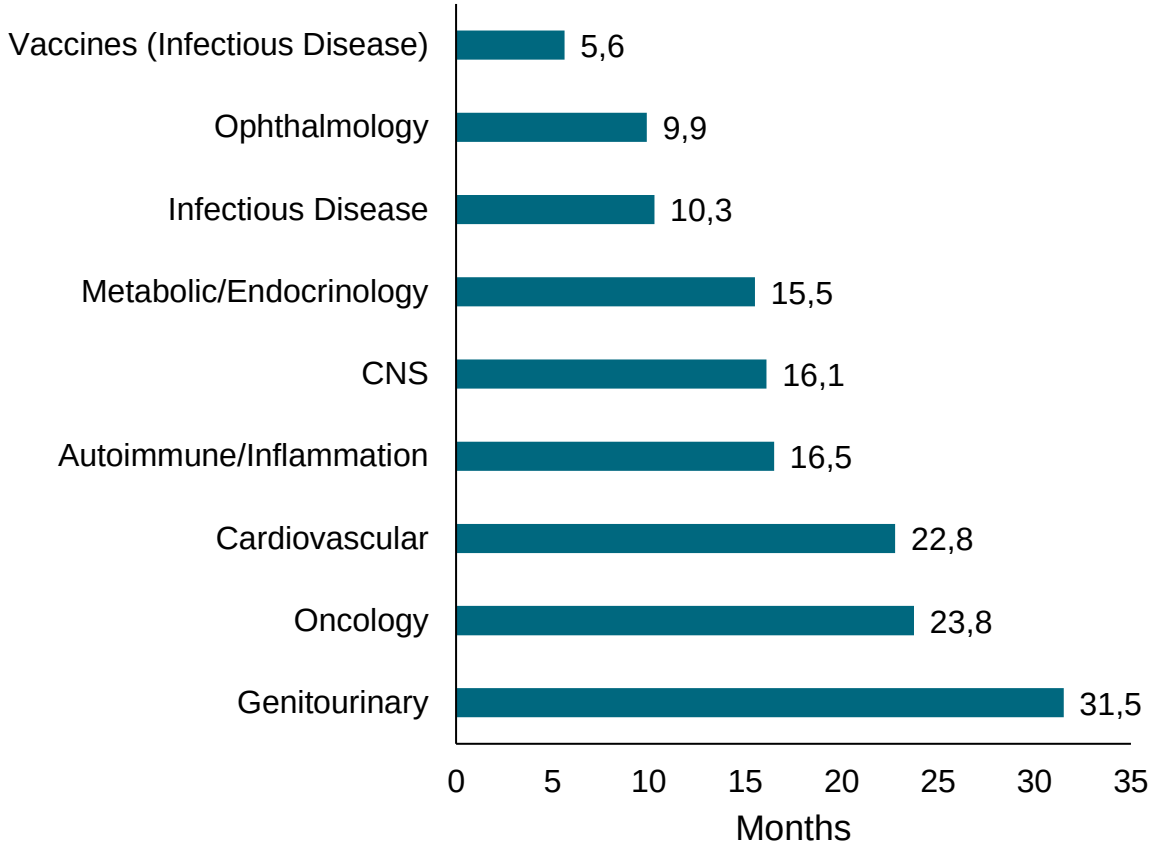
NB: Only single-country trials included in this analysis; Actual enrolment durations only; All trial phases included; trial start dates 2018-2022; No COVID-19 trials are included in the analysis

Sources: Citeline| Trialtrove; NB: Only single-country trials included in this analysis

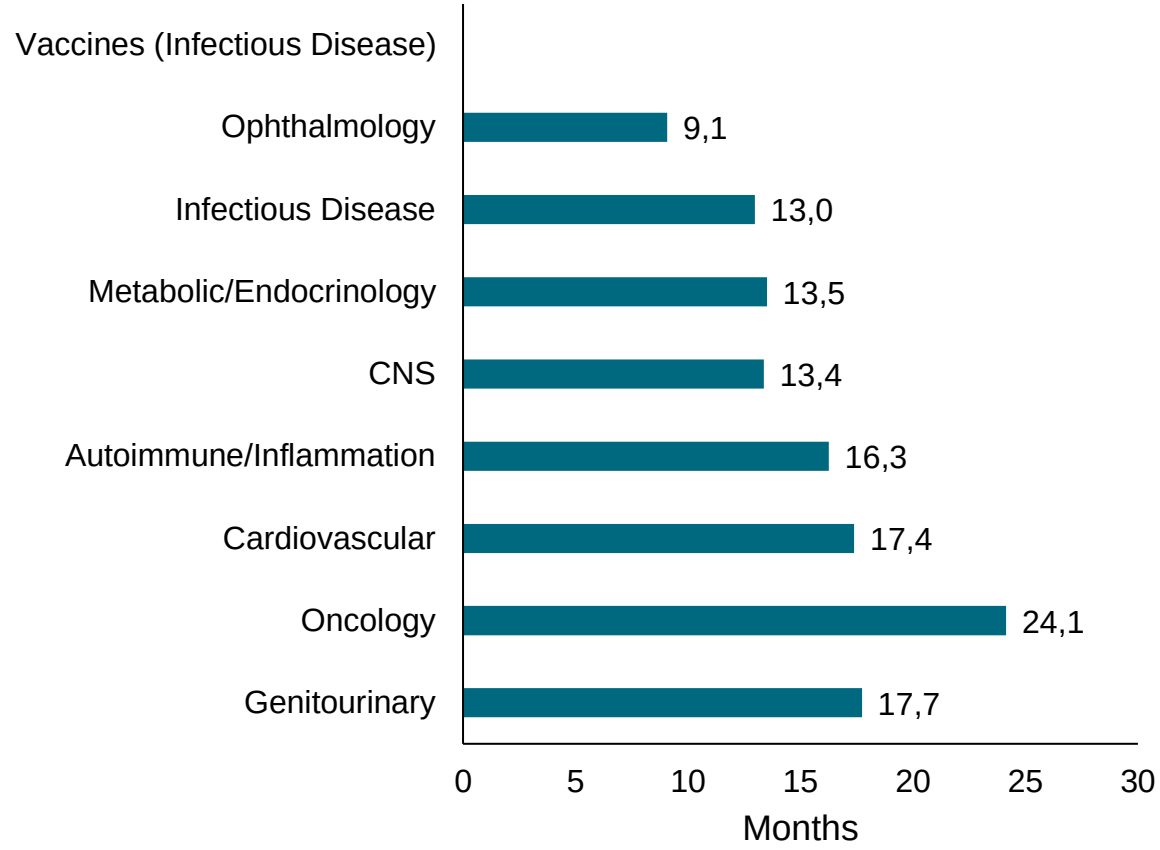
Enrolment duration by TA – Netherlands vs Spain

The Netherlands beats Spain in infectious disease and oncology; the countries have similar enrolment durations in the areas of ophthalmology and autoimmune/inflammation

Netherlands enrolment duration



Spain enrolment duration



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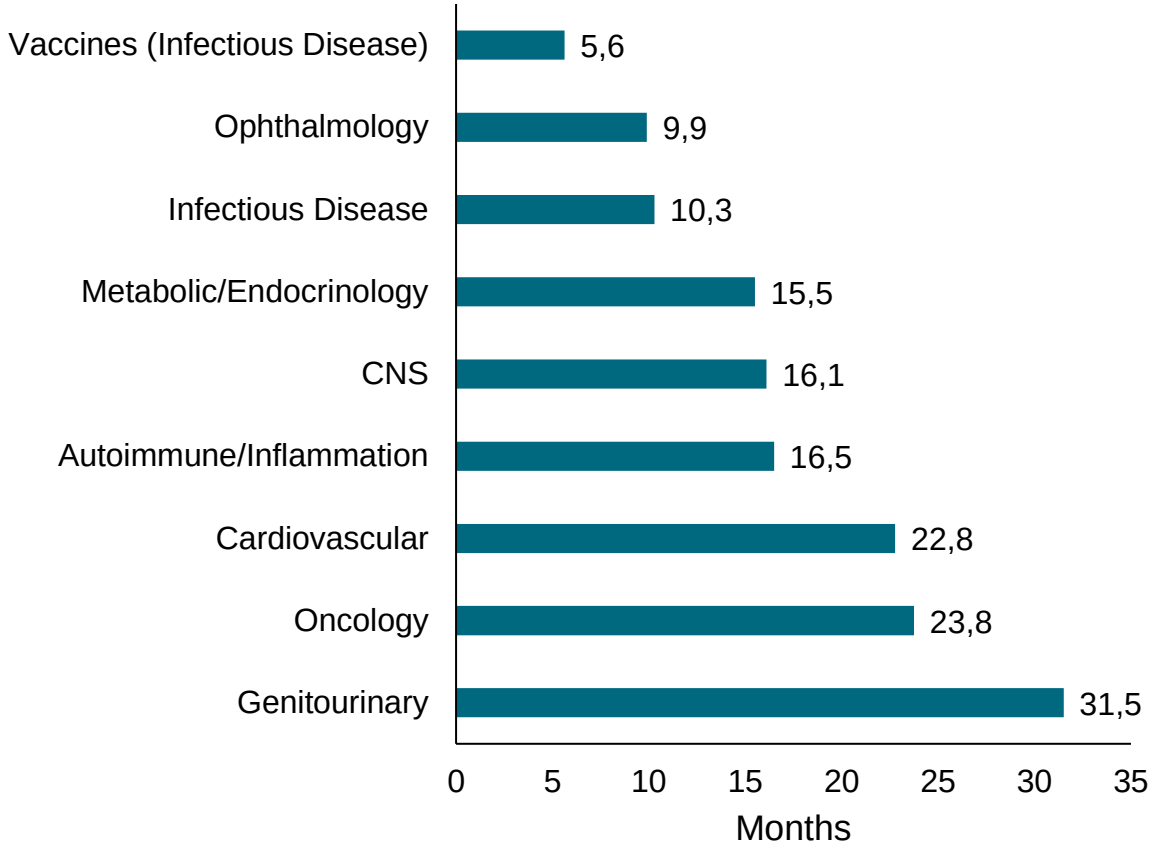
Sources: Citeline| Trialtrove; NB: Only single-country trials included in this analysis

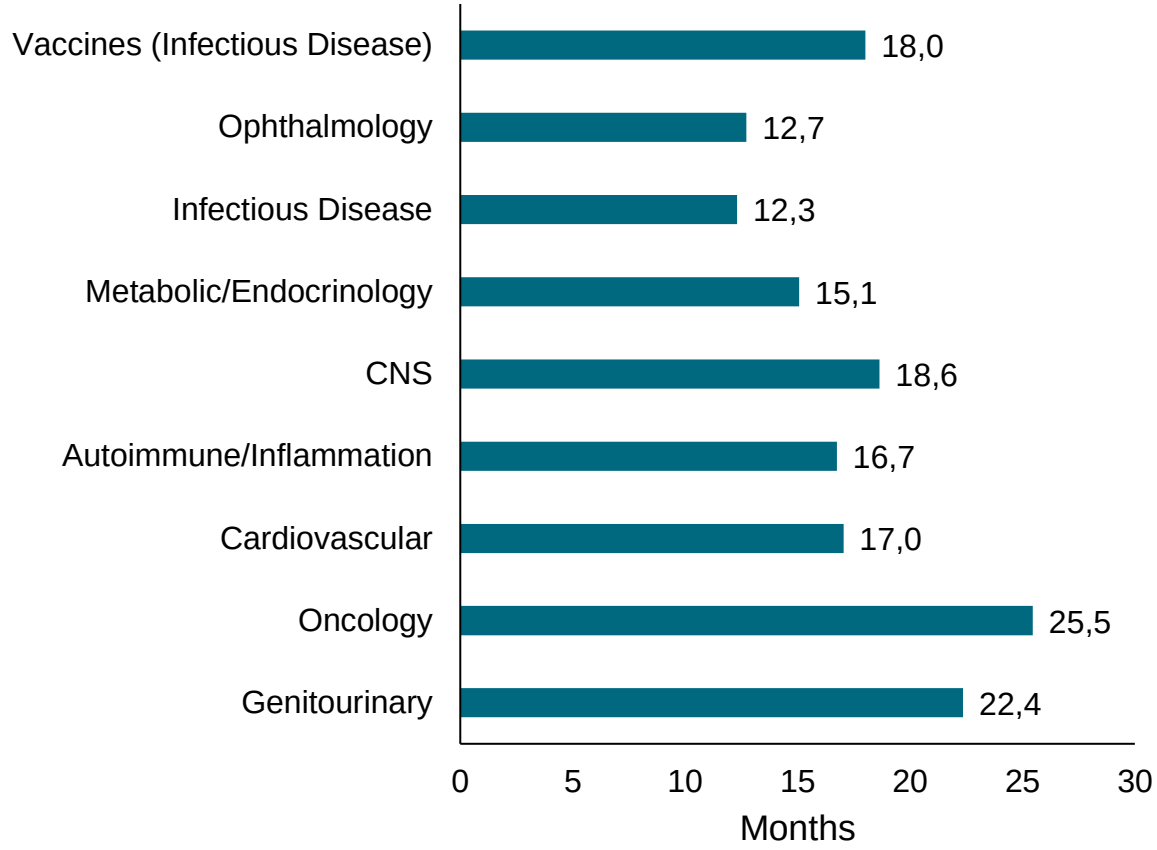
Enrolment duration by TA – Netherlands vs UK

The Netherlands has shorter enrolment in 6 of the 9 TAs with the UK taking less time for metabolic/ endocrinology, cardiovascular and genitourinary trials

Netherlands enrolment duration



UK enrolment duration

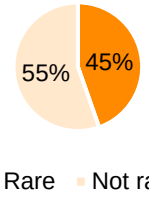
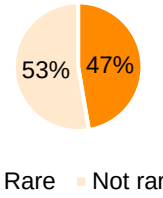
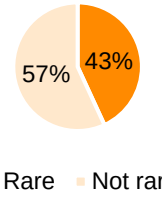
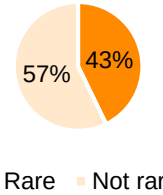
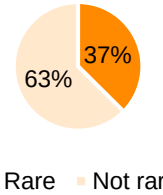
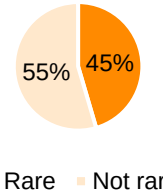
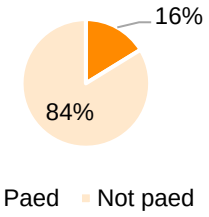
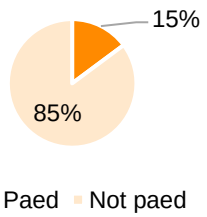
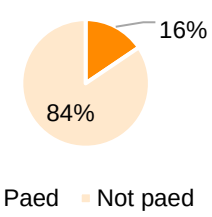
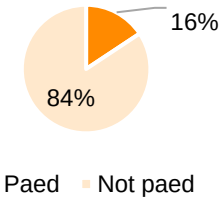
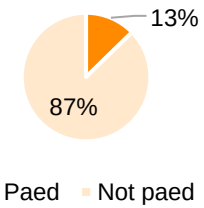
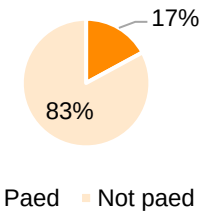
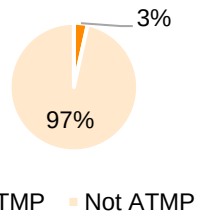
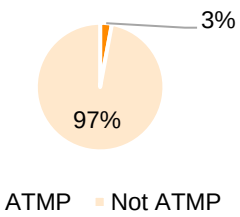
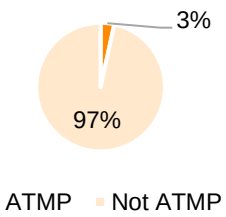
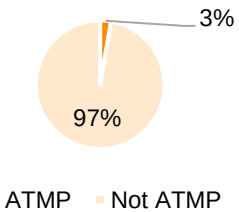
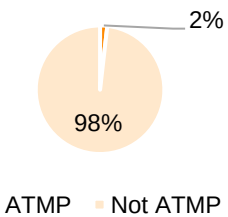
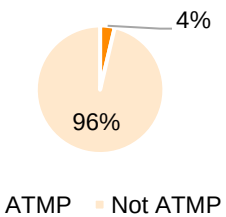
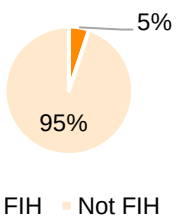
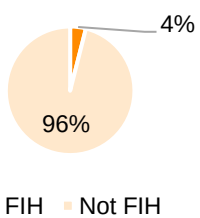
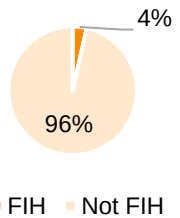
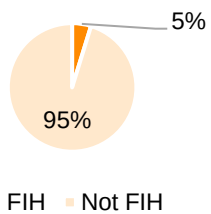
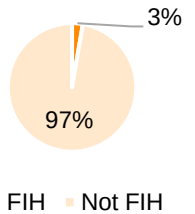
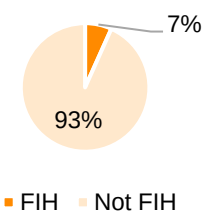


NB: Only single-country trials included in this analysis; Actual enrolment durations only; All trial phases included; trial start dates 2018-2022; No COVID-19 trials are included in the analysis

Sources: Citeline| Trialtrove; NB: Only single-country trials included in this analysis

Comparison of rare disease, paediatric, ATMP, and FIH trial proportions

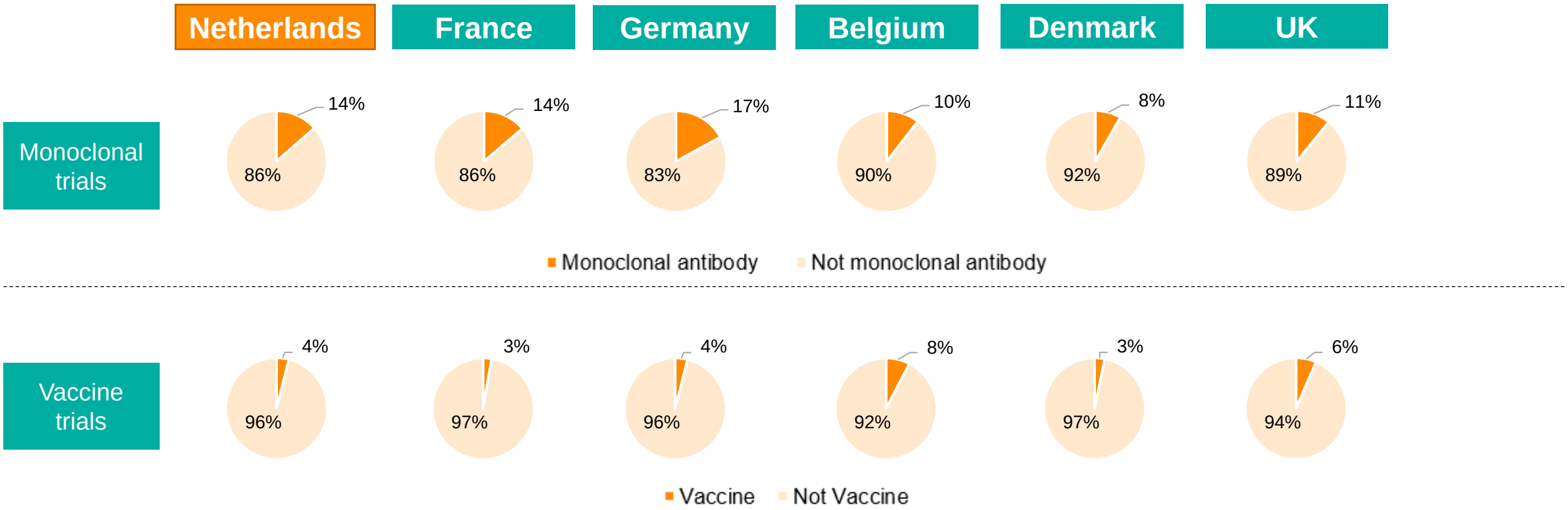
The proportions in the Netherlands are consistent with those in the comparator countries; the Netherlands hosts average proportions of ATMP & FIH trials, but is joint 2nd for proportions of rare disease trials (~50%)

	Netherlands	France	Germany	Belgium	Denmark	UK
Rare disease trials						
Paediatric trials						
ATMP trials						
FIH trials						

Sources: Citeline| Trialtrove

Proportion of trials studying mAbs and vaccines

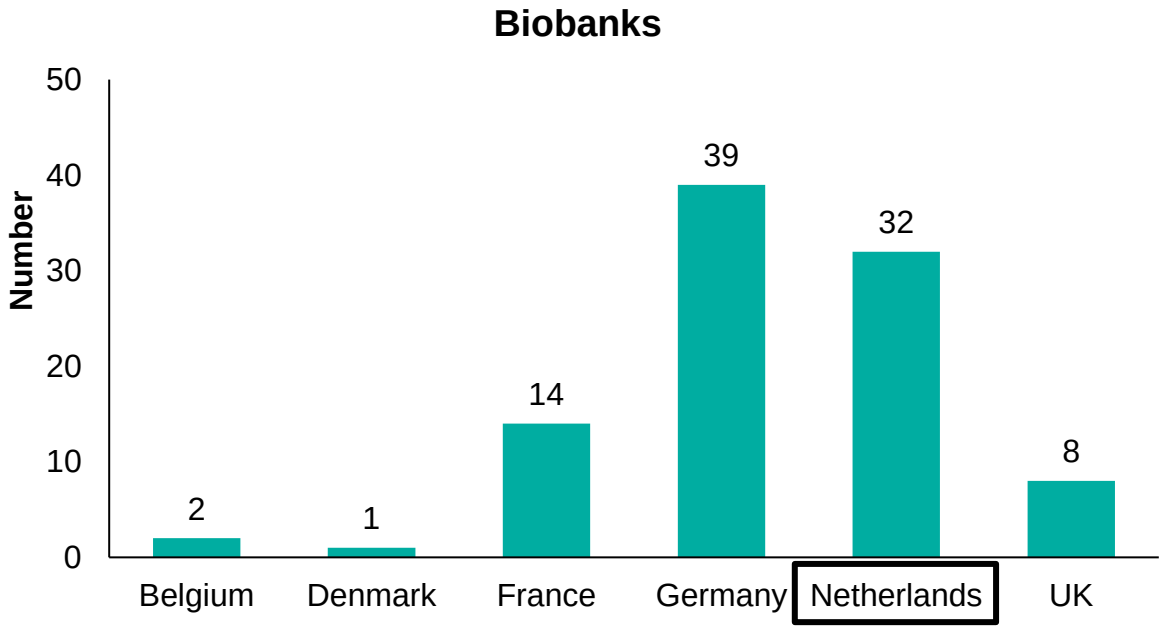
The Netherlands is joint 2nd with France in terms of monoclonal antibody trial proportions; for vaccine trials it is joint 3rd place ahead of France and Denmark

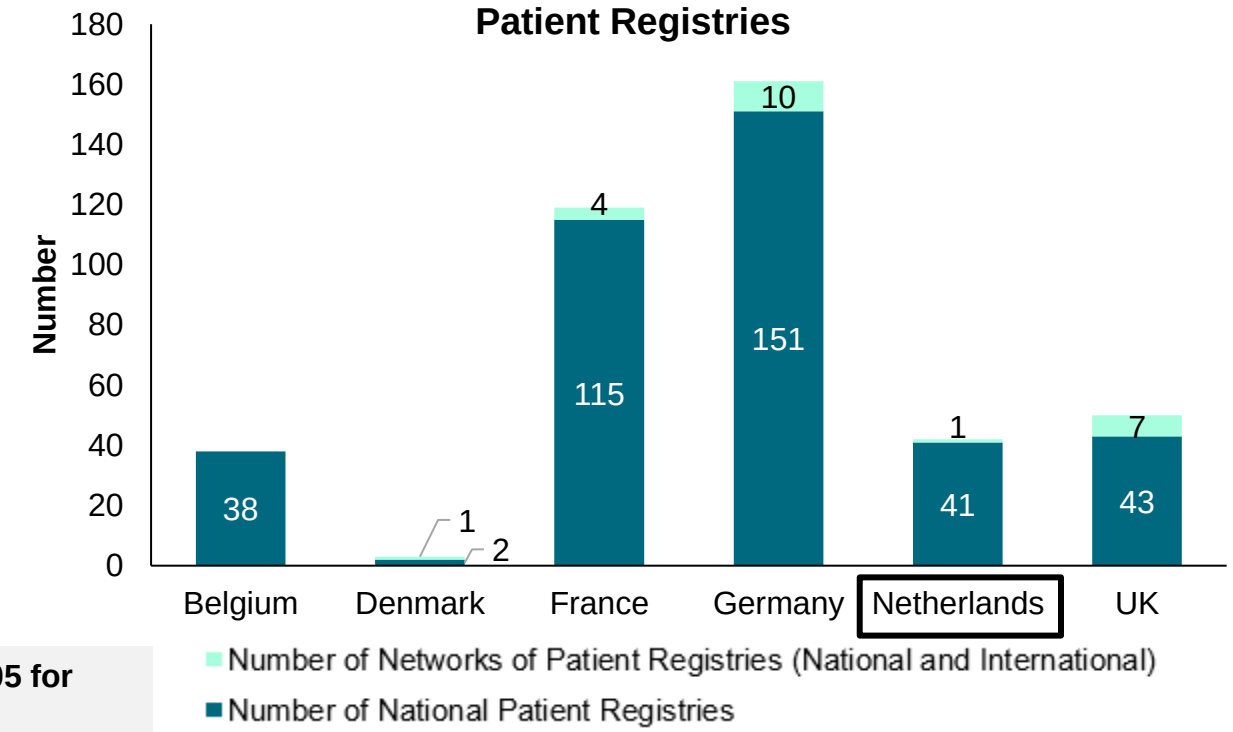


Sources: Citeline| Trialtrove

Availability of rare disease biobanks and patient registries

The Netherlands ranks 2nd (behind Germany) in the number of *Orphanet* rare disease biobanks and registries but leads when considering biobanks per capita





- The Netherlands leads with **0.18 biobanks per 100K of the population vs 0.05 for Germany**

"With biobanking, we perform well in the Netherlands. We lack the registries, so it would also be beneficial if we would establish more registries" – ***Key player 1***

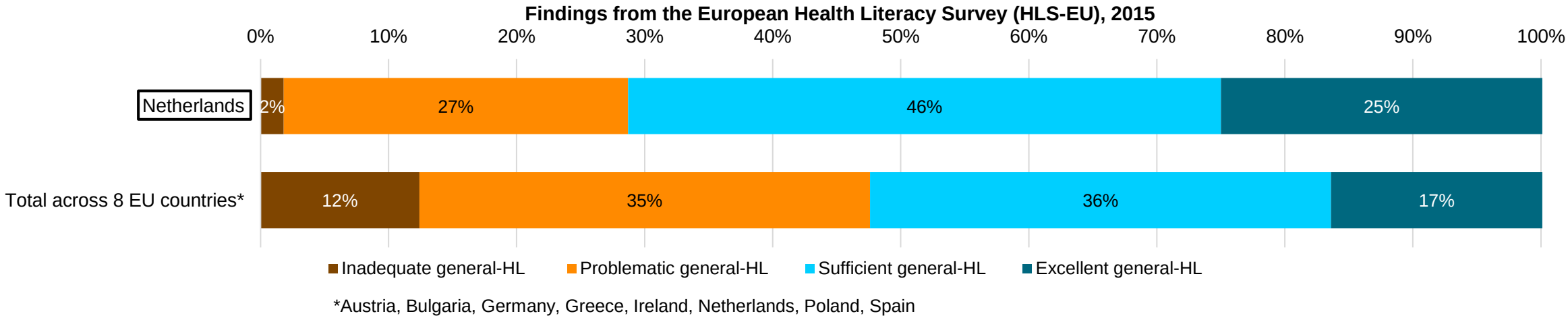
"The data is there but we are not using the data optimally, we need to bring the different data stakeholders together" – ***Key player 2***

Country specific biobank overviews can be found in the appendix

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

Education on health and clinical research (1/2)

Compared to the average across 8 EU countries, the Netherlands has the higher proportion of respondents with sufficient and excellent health literacy



The matrix of factors on which the survey questions were based:	Access/ find/obtain information relevant to health	Understand information relevant to health	Appraise/ judge/evaluate information relevant to health	Apply/use information relevant to health
Healthcare	Ability to access information on medical and clinical issues	Ability to understand medical information and derive meaning	Ability to interpret and evaluate medical information	Ability to make informed decisions on medical issues
Disease prevention	Ability to access information on risk factors for health	Ability to understand information on risk factors and derive meaning	Ability to interpret and evaluate information on risk factors for health	Ability to make informed decisions on risk factors for health
Health promotion	Ability to update oneself on determinants of health in the social and physical environment	Ability to understand information on determinants of health in the social and physical environment and derive meaning	Ability to interpret and evaluate information on health determinants in the social and physical environment	Ability to make informed decisions on health determinants in the social and physical environment

Source: 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)
Abbreviations: HL = Health Literacy

Education on health and clinical research (2/2)

Networks and plans exist to improve health literacy, and the access and understanding of healthcare information; as exemplified in France, better health literacy seems to correlate with more positive clinical trial attitude

Netherlands

The Dutch Health Literacy alliance began in 2010 and was started by a group of researchers & healthcare providers to highlight the problem of limited health literacy

It now has 80 partner organisations and includes a working group dedicated to patient experiences and participation

Belgium

33% of those above age 15 have low health literacy

The Belgium Health Care Knowledge Centre formed an action plan based on lessons learned from other countries, they focus on: governance, healthcare workforce development, partnerships with civil society, and organisational & institutional capacities

Denmark

The Danish Health Literacy Network launched a joint initiative with the Danish Society of Public Health in 2019 to improve health literacy

France

Of 1003 French adults questioned during the COVID-19 pandemic:

19.5% were very/extremely familiar with clinical trials, while 45.3% were somewhat familiar 8.2% had a negative opinion towards trials and 72% had a positive opinion.

A strong association was found between positive opinions & familiarity, and good health literacy

Germany

Germany has a National Health Literacy Action plan which contains 15 recommendations covering:

promotion of health literacy, making the health system user-friendly, living with chronic illness, and researching health literacy

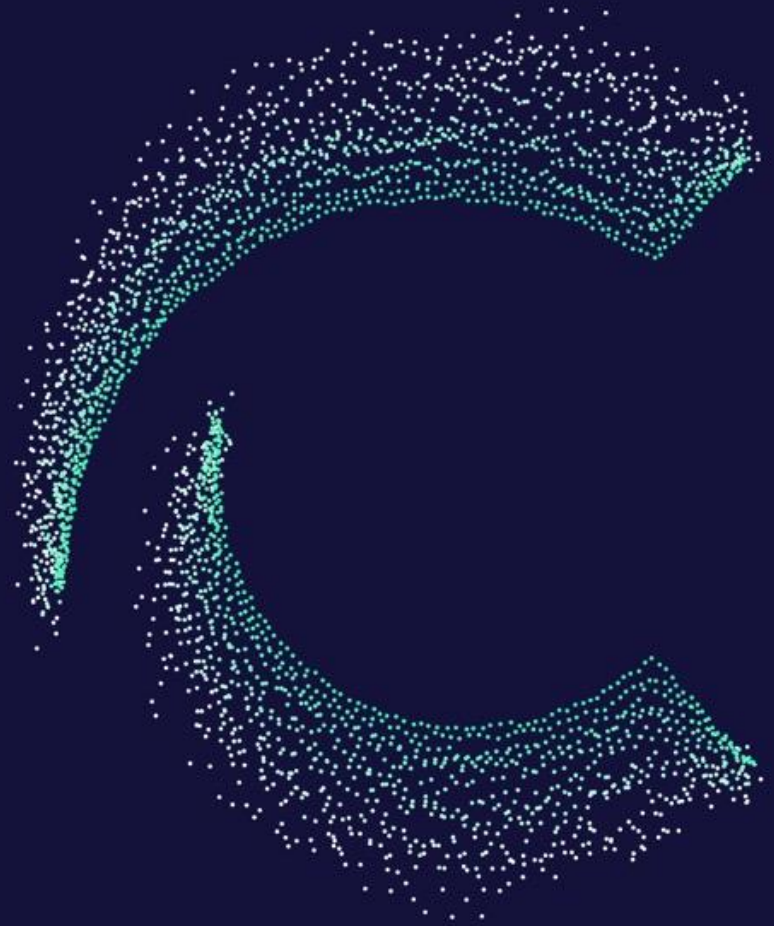
United Kingdom

The National Health Service (NHS) has a “Be Part of Research” service which helps patients find and participate in healthcare research, but also educates on current research taking place

Source: Sørensen et al., Work in progress: a report on health literacy in Denmark and the Netherlands, 2020; National Action for Health Literacy (Germany); Schultz et al., Int J Environ Res Public Health, 2021; NHS, Be Part of Research; KCE; For a Healthy Belgium

CITELINE

5. Future considerations & key player expectations



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

SWOT analysis – future considerations

The Netherlands is an attractive country for early phase rare disease trials due to the abundance of registries, founder mutations & physical infrastructure' these TAs should be a focus for future opportunities

Strengths

- Genetic research at academic hospitals
  - Genome of the Netherlands (GoNL) project
- Early-phase rare disease trials
  - Several registries in place
  - Princess Maxima centre – combination of 8 academic hospitals offers uniquely integrated patient care, research & training

Weaknesses

- Small population size makes the country an inappropriate location for single country trials
  - Approximately 70% of trials run in the Netherlands are multinational

Opportunities

- High prevalence of founder mutations (a disease mutation traced back to a common founder in the Netherlands or when the mutation was reported only among Dutch people)
  - Includes oncology and neurology diseases
- More niche & personalised medicine trials
  - Key players think the Netherlands' small size makes it ideal to pilot partially-decentralised trials, where therapeutic areas allow
- Strong presence in oncology, cardiology & CNS

Threats

- Privacy laws decrease ease of access to patient data
- Availability of professionals
  - Particularly in legal & contracting roles
- Bureaucracy within academic hospitals
- Cautious approach to collaboration with industry

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

Dutch clinical trial landscape in the next five years

Key players expect the Dutch clinical trial landscape to focus more on CNS diseases, ATMPs, and immunology as sponsors' funding grows and the therapy increasingly targets specific patient populations

Expected changes to the Dutch landscape in next 5 years

- More niche trials and personalised medicine trials
- Enhanced collaboration with healthcare professionals and better process alignment within and between academic hospitals
- Trials targeting specific groups of patients
- Strong presence in oncology, cardiology, and CNS (Alzheimer's, Parkinson's, and ALS), with potential growth in immunology
- Not attractive for single-country trials due to population size, but investigator-sponsored trials can be successful

"I think the ATMP field is a good example of what the Netherlands can be strong in." **– Key player 6**

"…better collaboration with healthcare professionals and better alignment within, and between, the academic hospitals" **– Key player 1**

"I would expect the development of protocols which are searching for more specific patients. That depends on whether the biobanks are accessible to investigators" **– Key player 2**

"The Netherlands will stay strong in oncology and cardiology. We see a lot more activity in neuroscience as it is still not being tackled on a global level. Immunology will grow because most of the pharmaceutical companies are investing quite heavily in that area as well" **– Key player 3**

"Netherlands is not an attractive country for mono studies. Multinational investigator-sponsored trials yes, but mono no. We don't have the population." **– Key player 4**

The Netherlands for personalised medicine trials

- The Genome of the Netherlands (GoNL) project is a consortium of several universities and academic hospitals with the aim of identifying genetic variations in the Dutch indigenous population
  - The project was initiated by the Dutch biobank collaboration BBMRI-NL
  - The project helps to extract useful biomedical information which is useful for the development of new treatments and diagnostic techniques
    - ➢ The Netherlands is well positioned to host these trials

The consensus was that same approach would be taken across other EU countries

Source: Citeline Primary Research. Key players were interviewed for their insights, n=6; Genome of the Netherlands

Foreseen barriers in improving clinical attractiveness in the Netherlands

Key players identify resource availability, privacy laws, and lack of collaboration between industry and hospitals as the main barriers to improving clinical trial attractiveness

Privacy Laws

- Privacy laws and optimising electronic data records present challenges in facilitating communication and access to patient information for investigators

"We need to go to the universities, promoting the facts of clinical research and the life science in general." – ***Key player 3***

Collaboration

- Lack of emphasis on collaboration with industry in the educational system pose a barrier to public-private collaborations
- Bureaucracy within hospitals, specifically with aligning hospital boards and fostering collaboration, is identified as a main barrier

"GPs need to be able to communicate easier with hospital records. If optimised, then it gives investigators easier access to understand how many patients they truly have"– ***Key player 2***

Resources

- Two key players highlighted that the availability of professionals would be a bottleneck
- However, efforts are being made to address the issue of the lack of dedicated professionals through stakeholder engagement and efficient resource allocation

"The main barrier is getting all those hospital boards aligned and working together to make it more attractive"– ***Key player 6***

Nurse shortage

- Worldbank data shows the number of nurses & midwives per capita has declined/ remained flat for recent available years for Belgium, Denmark, the UK, and the Netherlands; only Germany and France have seen meaningful increases
  - 2022 data of the Dutch healthcare sector showed 61,000 vacancies, the largest shortage is among nurses - this shortage is seen at the EU level

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

Future clinical trial trends in the Netherlands

The Netherlands is attractive for rare disease trials due to knowledgeable key opinion leaders, strong infrastructure and dedicated registries; fully decentralised trial adoption is both unlikely and not preferable

Decentralised Clinical Trials
Fully decentralised trials adoption in the Netherlands is unlikely, but aspects such as wearables and local blood draws are seen as potential decentralisation elements that could be utilised
The Netherlands is small and has a good travel network; therefore, patients and specialists (especially oncologists) prefer on-site visits
The push for decentralisation is likely to come from sponsors and CROs
Key players believes that the Netherlands' small size makes it ideal to pilot decentralisation, and that the country is open to innovation

"Fully decentralised? No. Oncologists especially want to see their patients, they want to look them in the eye." ***– Key player 1***

"I'm quite impressed about the registries that are in place, but also the passion and the dedication of a lot of scientific leaders to make sure that those rare diseases are being tackled. The Princess Maxima Centre for paediatric oncology, wow, they are fantastic" – ***Key player 3***

"Easy accessibility of all the stakeholders in the field makes us the ideal place to pilot eConsent and eISF. I think we have the highest adoption of internet access on a global level. Dutch people really would like to have that innovation and would like to pilot that." ***– Key player 3***

Rare Disease Trials
Four key players believe that the Netherlands is attractive for rare disease clinical trials due to strong network of KOLs and dedicated registries
The Netherlands is particularly attractive for early-phase rare disease trials. However, challenges may arise in larger-scale trials due to population size limitations
The Netherlands has founder mutations of certain rare diseases, e.g., Sanfilippo disease and juvenile neuronal ceroid lipofuscinosis, that are advantageous for rare disease trials
Further founder mutations have been identified within hereditary ovarian-breast cancer and frontotemporal dementia

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

Advice to sponsors that are new to initiating trials in the Netherlands

Key players advise that sponsors should initiate recruitment discussions early, collaborate with CROs, keep communication direct and utilise the Central Committee resources when starting trials in the Netherlands

Direct, clear and timely communication

Keep protocol simple

Work with experienced CROs

Start recruitment discussions early

Leverage CCMO website for guidance

Invest in personal collaboration

"Try to find an experienced CRO to keep timelines in control, be aware of the new CTR trial regulations Be aware that there is a (worldwide) upcoming shortage of dedicated trial personnel"
– Key player 5

"I think that personal collaboration is really good. So, invest time in people, not just remote relationships, but visit and take time for that, certainly in the beginning."
– Key player 2

"Start thinking about and discussing recruitment as soon as possible because that is typically done too late. Also, very early on in the process, get information on the specifics of the Netherlands with regard to approval and also learn. So, make use of the knowledge and the know-how that is within the research institutes about this approval" ***– Key player 1***

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

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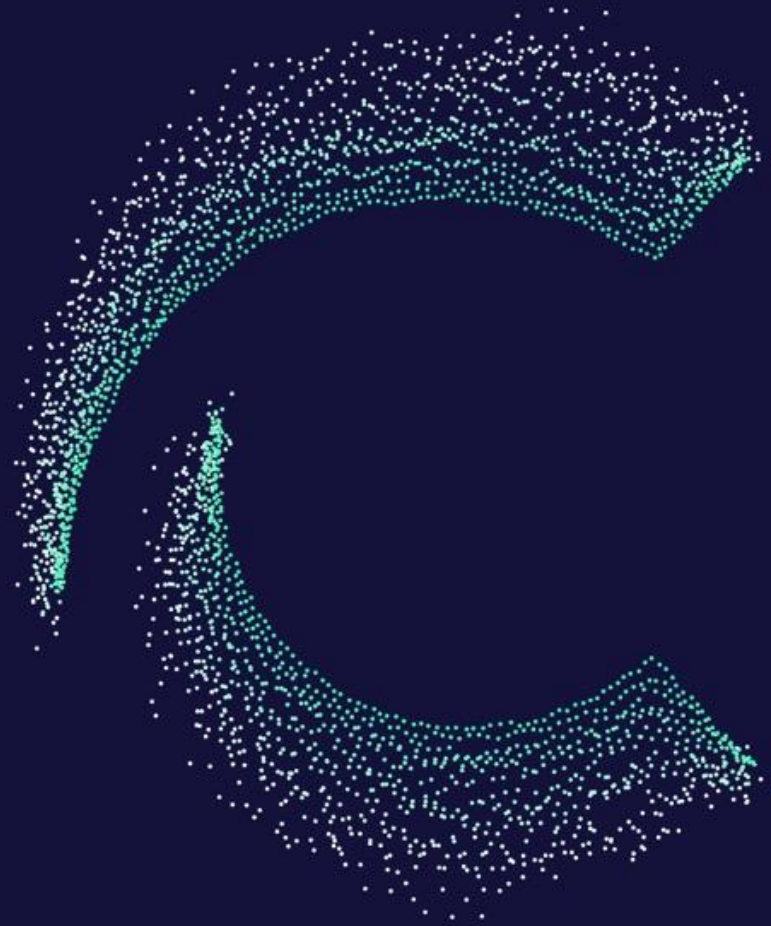
6. Abbreviations



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

Abbreviations List

Abbreviation	Meaning
ALS	Amyotrophic Lateral Sclerosis
ATMP	Advanced Therapy Medicinal Products
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

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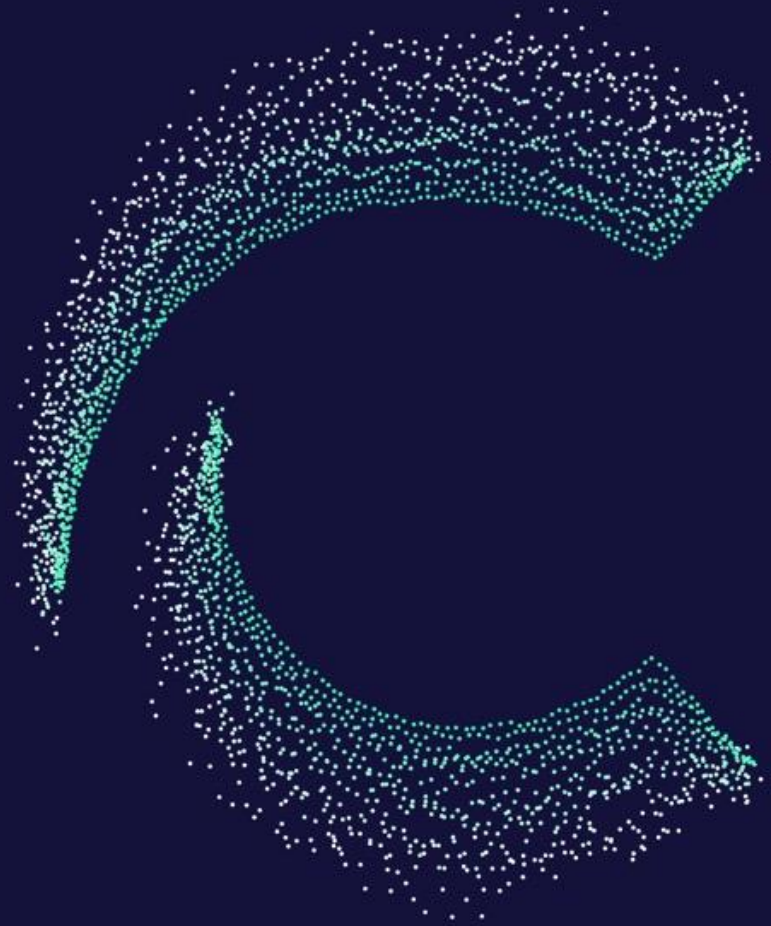
7. Appendix



Accessibility of scientific advice in Belgium

Although most requests (just under 58%) are from large commercial applicants, a 75% reduction in advice fees is available for smaller researchers such as SMEs and universities

National Competent Authority Scientific Advice

Details	▪ Advice is provided for all sponsor types from pharmaceutical/biotech companies to smaller research centres ▪ In 2020: • The majority (just under 58%) of applicants for scientific advice were commercial (non-SME) applicants • 57% of advice requested was for bio(techno)logical products while 15% were for ATMPs • 48% of advice was requested at Phase 1 • A third of requests were COVID-19 related, and of that third, 35% were Simultaneous National Scientific Advice (SNSA) requests
Transparency	▪ The National Innovation Office and Scientific Technical Advice Unit of the Directorate General PRE offers a "centralised and transparent" service ▪ It also assures full confidentiality and manage conflict of interest of the experts providing the advice ▪ Belgium is transparent with statistics on the types of advice requests- with the data readily available on the FAMHP scientific advice site
Exemptions from frees	▪ 75% reduction on rates are available for SMEs, universities, certified hospitals, public utility foundations, and statutory administrations. ▪ An exemption to planned clinical trials is also available for applicants who submit request for approval within 2 years of receiving the advice

Member of ECRIN?: **No**

The European Clinical Research Infrastructure Network (ECRIN) works with national networks of clinical trial units and European correspondents to facilitate researchers in conducting multinational European clinical trials, focussing on investigator-sponsored clinical trials

Member of SNSA?: **Yes**

- In 2020 only **22% of requests were SNSA requests** as opposed to just National scientific advice requests in Belgium

Scientific National Advice Service (SNSA) pilot, launched by the EU-Innovation Network is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously (i.e., from each member state in which they plan to conduct their trial) to enhance the quality and consistency of advice)

Other Organisations of note for Scientific Advice

Belgian Healthcare Knowledge Center	▪ (aka KCE) Is an independent research centre that provides advice on healthcare related topics to create validated working methods for healthcare workers and public health researchers
Healixia	▪ A community of professionals formed in 2020 who are active in all stages along the life cycle of medicines. This community consists of the following groups: Belgian Regulatory Affairs Society, Belgian Association of Pharmaceutical Physicians, Belgian Association of Phase I Units, and the Belgian Association of Clinical Research Professionals
Belgian Association of Research Ethics Committee (BAREC)	▪ BAREC is an association to encourage exchange of knowledge between ethics committees and to form advice, providing the ethics committees with a voice
National Institutes/Disease Foundations	▪ Belgium has multiple disease-specific foundations that can provide resources for clinical research e.g. the Belgian Society of Cardiology and the Belgian Association for Metabolic Diseases

Sources: FAMHP; FAMHP Statistics; KCE; Healixia; BAREC; Belgian Society of Cardiology; Belgian Association for Metabolic Diseases; ECRIN; SNSA

Accessibility of Scientific Advice in Denmark

Denmark benefits from a strong, centred source of clinical trial support and networking in the form of Trial Nation Denmark, as well as high transparency of the medical data used to inform the DMA's scientific advice

National Competent Authority Scientific Advice

Details	▪ In 2018 the Danish Medicines Agency (DMA) created a new concept for providing scientific advice to companies and smaller researchers, as part of the wider initiative of the growth team for life sciences that was established by the Danish Medicines agency in 2016. ▪ The new aim of the new offering was to introduce more prioritised competent scientific advice, leaning on already achieved investigational results as well as advising on future development programs
Transparency	▪ The Danish Medicines Agency has high data transparency due to its Data Analytics Centre, which aims to transform information and data related to medicines and medical devices into knowledge that can assist the DMA with providing scientific advice ▪ Examples include being transparent with how data analyses are prioritised, which analyses have been conducted, and which analysis projects are upcoming
Exemptions from fees	▪ No reductions or exemptions apply to the fees, and there is no special concession for SMEs and hospital-based researchers

Member of ECRIN?: No

The European Clinical Research Infrastructure Network (ECRIN) works with national networks of clinical trial units and European correspondents to facilitate researchers in conducting multinational European clinical trials, focussing on investigator-sponsored clinical trials

Member of SNSA?: Yes

Scientific National Advice Service (SNSA) pilot, launched by the EU-Innovation Network is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously (i.e., from each member state in which they plan to conduct their trial) to enhance the quality and consistency of advice

Other Organisations of note for Scientific Advice

Trial Nation Denmark	▪ A single national source for both researchers (including companies and clinical researchers) and patients who are looking to sponsor or participate in clinical trials in Denmark respectively. ▪ It operates using 8 national clinical centres (each associated with a different therapy area) and networks, and 1 medtech centre
National Institutes/Disease Foundations	▪ Denmark also has a few disease-specific foundations that can provide resources for clinical research e.g. Rare Diseases Denmark

Sources: DMA; Trial Nation Denmark; DMA's Data Analytics Centre; DMA New Scientific Advice Concept; Rare Diseases Denmark; ECRIN; SNSA

Accessibility of scientific advice in France

France has a very organised and expansive research network in the form of the French Clinical Research Infrastructure, and trial sponsors benefit from ANSM's free scientific advice

National Competent Authority Scientific Advice	
Details	▪ Specific issues regarding preclinical, clinical, quality, and both safety and efficacy can be addressed with scientific advice across all therapeutic areas ▪ The advice can be requested at any stage of product development, before filing for market authorisation, and in the post-authorisation phase (e.g. in the case of new indications)
Transparency	▪ No clear statement of confidentiality or transparency of the advice and information provided by applicants is made and no statistics are made available on the types of advice that are requested by the applicants
Exemptions from fees	▪ Advice from the ANSM is free

Member of ECRIN?: Yes

The European Clinical Research Infrastructure Network (ECRIN) works with national networks of clinical trial units and European correspondents to facilitate researchers in conducting multinational European clinical trials, focussing on investigator-sponsored clinical trials

Member of SNSA?: Yes

Scientific National Advice Service (SNSA) pilot, launched by the EU-Innovation Network is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously (i.e., from each member state in which they plan to conduct their trial) to enhance the quality and consistency of advice

Other Organisations of note for Scientific Advice	
French Clinical Research Infrastructure Network	▪ This collaboration comprises 16 clinical investigation networks across multiple therapeutic areas (including retinal diseases, vaccinology, auto-immune and auto-inflammatory diseases), 3 networks of expertise and methodology (rare disease, epidemiology, and medical devices), and 1 support platform which provide all services need to support a clinical trial ▪ It's a national infrastructure for clinical trials to encourage collaboration, and is the scientific partner in France for the ECRIN
Haute Autorite De Sante (HAS)	▪ One of the missions of this body is to encourage early conversations to occur with companies developing medicinal products to provide recommendations on pivotal studies as well as assist with HTAs

Sources: ANSM; ECRIN; SNSA; French Clinical Research Infrastructure Network; HAS

Accessibility of scientific advice in Germany

Similarly to Belgium, the BfArM releases some statistics to provide insight into the numbers and types of advice requests they receive; Germany also benefits from the KKSN network of clinical research centres

National Competent Authority Scientific Advice

Details	▪ For medicinal products, advice is available in 3 main ways: 1. During development (scientific advice): this is any time before the initial authorisation of the medicine and could cover a range of things, including non-clinical investigations, pharmacovigilance, and pharmaceutical quality 2. Prior to a clinical trial application: pre-CTA advice relates to a specific CTA that is planned 3. Or prior to a marketing authorisation application: relating to a concrete MAA, discussing topics such as legal elements, procedure, and labelling
Transparency	▪ The BfArM is transparent with the types of scientific advice requests received as they make some statistics easily available. ▪ In 2022: • There were 290 scientific advice requests (the lowest annual total since 2014) • 16 of the 209 requests were early benefit advice requests (consultations on benefit assessment) • The BfArM took over 138 of the 833 EMA's Scientific Advice Working Party (SAWP) scientific advice procedures
Exemptions from fees	▪ No exemptions or reductions noted

Member of ECRIN?: Yes

The European Clinical Research Infrastructure Network (ECRIN) works with national networks of clinical trial units and European correspondents to facilitate researchers in conducting multinational European clinical trials, focussing on investigator-sponsored clinical trials

Member of SNSA?: Yes

Scientific National Advice Service (SNSA) pilot, launched by the EU-Innovation Network is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously (i.e., from each member state in which they plan to conduct their trial) to enhance the quality and consistency of advice

Other Organisations of note for Scientific Advice

Technology, Methods and Infrastructure for Networked Medical Research (TMF)	▪ A network bringing together researchers across Germany and across a range of different disciplines to improve and provide solutions for challenges in medical research
Initiative of German Practice-Based Research Networks – DESAM-ForNet	▪ A combination of 6 practice-based research networks
KKS-Netzwerk (KKSN)	▪ Scientific partner in Germany of the ECRIN ▪ The KKSN is a network of centres which co-ordinate for clinical trials, and comprises 27 academic coordinating centres across Germany, including universities, university hospitals, and medical faculties ▪ The network allows collaboration between study centres for multicentre trials, enables training, and provides clinical trial design and delivery support, through the exchange of facilities and expertise

Sources: ECRIN; SNSA; BfArM; Scientific Advice Working Party; TMF; Initiative of German Practice-Based Research Networks – DESAM-ForNet; KKSN

Accessibility of scientific advice in the United Kingdom

Although not part of some of the main EU-wide networks, the UK has a large national network of Clinical Research Units, which includes a Study Support Service

National Competent Authority Scientific Advice	
Details	▪ Advice is provided by the MHRA at all stages of initial product development, before a marketing authorisation application, and during the pre-submission period for a variation to an existing marketing authorisation ▪ Beyond matters of, for example, non-clinical elements, clinical elements, quality aspects and pharmacovigilance, a broader scope meeting is also possible for requests that are not specific to a product (e.g. choice of endpoints or risk management plans) ▪ Joint advice meetings between the MHRA and the National Institute for Health and Care Excellence (NICE) are also available, with the further option of input from the Clinical Practice Research Datalink (CPRD), which collects patient data for public health and clinical studies
Transparency	▪ No clear statement of confidentiality or transparency of the advice and information provided by applicants is made and no statistics are made available on the types of advice that are requested by the applicants
Exemptions from fees	▪ Exemption from fees is available for UK-based small and medium sized companies

ecrin **Member of ECRIN?:** **No**

The European Clinical Research Infrastructure Network (ECRIN) works with national networks of clinical trial units and European correspondents to facilitate researchers in conducting multinational European clinical trials, focussing on investigator-sponsored clinical trials

HMA Heads of Medicines Agencies **Member of SNSA?:** **No**

Scientific National Advice Service (SNSA) pilot, launched by the EU-Innovation Network is aimed at facilitating applicants who wish to obtain scientific advice from more than one of the EU National Competent Authorities simultaneously (i.e., from each member state in which they plan to conduct their trial) to enhance the quality and consistency of advice

Other Organisations of note for Scientific Advice	
NICE	▪ National Institute for Health and Care Excellence ▪ Part of the Department of Health and Social Care, NICE provide national guidance and advice, assessing new drugs and creating evidence-based recommendations for healthcare in the form of national guidelines
NIHR's CRN	▪ The National Institute for Health and Care Research's (NIHR) Clinical Research Network (CRN) ▪ The CRN is made of 15 Local Clinical Research Networks (split by geographical location in the UK) which co-ordinate to support in the delivery of research across 30 specialities ▪ The CRN also have a Study Support Service which helps non-commercial researchers to carry out their research
National Institutes/Disease Foundations	▪ The UK has multiple disease-specific groups that can provide resources for clinical research e.g. National Organisation for Rare Disease, and in particular a large number of charitable disease foundations prominent in the research space e.g. Cancer Research UK, the British Heart Foundation, and the Chronic Disease Research Foundation

Sources: ECRIN; SNSA; MHRA; NICE; CPRD; NIHR CRN; Cancer Research UK; British Heart Foundation; Chronic Disease Research Foundation

Clinical research networks in Belgium

Like many other countries, Belgium has several networks dedicated to specific diseases; notably, Belgium and the Netherlands have been collaborating since 2000 on the Belgian–Dutch Clinical Pathway Network

1979

SGPs - Network of General Practitioners

About 120 general practices all over Belgium who report data for 8 different health problems on a weekly basis (infectious and non-infectious diseases)

The coverage of the network is estimated at 1.1% — 1.5% of the Belgian population

1988

European Society for Developmental Perinatal and Paediatric Pharmacology (ESDPPP)

ESDPPP promotes research in developmental perinatal and paediatric pharmacology and offers a forum for dialogue between pharmacologists and clinicians interested in the effect of medicines in paediatric patients

2000

Belgian–Dutch Clinical Pathway Network (BDCPN)

Involved in over 1000 projects in 57 participating organisations across Belgium and the Netherlands

BDCPN currently counts 42 general hospitals, 3 psychiatric hospitals, 7 rehabilitation centres and 5 primary care organisations.

BDCPN supports multi-centre research projects and international collaboration

2009

The Belgian Paediatric Clinical Research Network (BPCRN)

Provides details of the centres which have the appropriate experience to carry out clinical trials involving children

BPCRN aims to lower the overall workload within similar trials (joint usage of templates, distribute preparational work among multiple sites

2016

KCE Trials Belgian Health Care Knowledge Centre

Created on the example of the HTA comparative effectiveness from NIHR in UK

KCE selects and funds large, multi-centre pragmatic randomised trials but does not conduct them

2022

Belgian Cancer Research Consortium

5 Belgian cancer research organisations cooperate in a network to leverage their work and enhance strategic collaboration between individual researchers and organisations

Sources: Sciensano; ESDPPP; BDCPN; BPCRN; KCE Trials; Belgian cancer research consortium; N.B. Not intended to be exhaustive

Clinical research networks in Denmark

In the last five years, the Danish landscape has been dominated by Trial Nation, a single-entry point that provides a national set up and governance for facilitating clinical trials

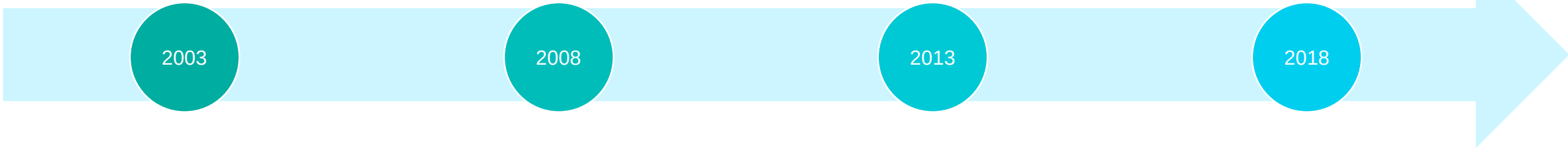
Trial Nation

Represents a strong and mutually beneficial partnership between Ministry of Industry, Business and Financial Affairs and the Ministry of Health, the 5 Danish regions, Life Science companies, patient organisations, Danish Medical Societies and thus provides advantage for both public and private stakeholders

Also provides good access to high quality professionals conducting early phase clinical trial

Danish Clinical Research Consortium (DCRC)

A national infrastructure which 'virtually' gathers and connects all Danish academic clinical research expertise



The Danish Clinical Research Infrastructures Network (DCRIN)

Danish national hub in ECRIN, to improve the quality of clinical research at a national and international level, promoting harmonised research procedures, reducing bottlenecks in administrative procedures, sharing expertise and facilitating multi-site studies, with particular benefit to disease conditions that are difficult to recruit participants

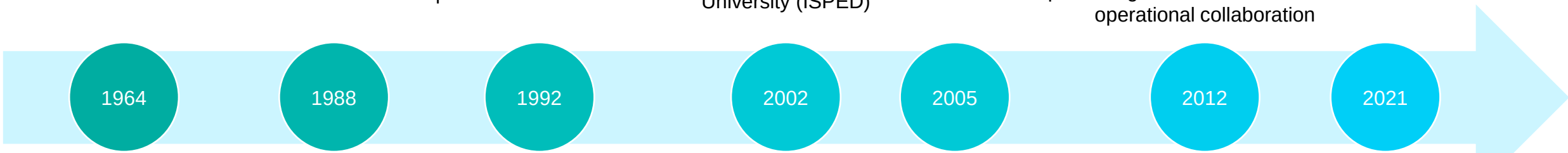
The Nordic Trial Alliance (NTA)

Designed to support Nordic clinical multi-centre trials

Sources: DCRIN; DCRC; NTA; Trial Nation; N.B. Not intended to be exhaustive

Clinical research networks in France

The French Clinical Research Network landscape spans over 59 years, indicating a long-standing and continuous recognition of the importance of collaborations fortified through network establishment



The National Institute of Health and Medical Research (INSERM)

Public scientific and technological institution solely focused on human health

Placed under the dual supervision of the Ministry of Health and the Ministry of Research

Each year INSERM coordinates more than 6,500 cooperation projects with foreign partners

National Agency for Research on AIDS and Viral Hepatitis (ANRS)

Federating, coordinating, leading and funding public research on HIV and viral hepatitis

INSERM Hospitals - Clinical Investigation Centers

Clinical Investigation Centers (CICs) are clinical research infrastructures made available to investigators to carry out their clinical and health research projects

The UEC Network (RFUEC [Réseau Français Des Unités d'Essais Cliniques])

Facilitate national and European collaboration, with an administrative affiliation to Institut de Santé Publique, d'Epidémiologie et de Développement Bordeaux-2 University (ISPED)

The National Research Agency (ANR)

Promote French research on projects, and to stimulate innovation by promoting the emergence of multidisciplinary collaborative projects and by encouraging "public-private" collaborations

French Clinical Research Infrastructure Network (F-CRIN)

French hub of ECRIN

Helps to unlock synergies between French clinical research players by promoting scientific excellence and operational collaboration

ANRS | Emerging Infectious Diseases

Integration the ANRS and the INSERM REACTing consortium into a new agency to optimize response to the pandemic crises

Facilitates several national and international networks of researchers and doctors employed by the principal research organisations, universities, hospitals, and associations

Sources: L'Agence nationale de la recherche (ANR), INSERM, ANSR, FCRIN, Demotes-Mainard J (2005) Clinical research infrastructures and networks in France: report on the French ECRIN workshop; NB not intended to be exhaustive

Clinical Research Networks in Germany

Since 2020, the focus in Germany has been promoting research and family medicine; the Federal Ministry of Education and Research is funding the "German Practice-Based Research Networks" initiative until 2025

21 Medical Competence Networks

Initiated and funded by the Federal Ministry of Education and Research (BMBF) to enable innovative multidisciplinary health research.

More than 400 clinical and epidemiological studies have been carried out and thus non-commercial clinical research in Germany significantly advanced

Funding ended in 2019 and since, many have been discontinued or running on donations or merged to form new networks

German Cancer Consortium (DKTK)

More than 20 academic institutions and university hospitals at 7 locations

The DKTK supports clinical studies of innovative therapeutic and diagnostic procedures

The DKTK's Joint Funding Program supports multicenter research projects and clinical trials

Around 50 joint funding projects have been launched within the DKTK since 2012

NRW-GPRN

Research network including 520 GP practices and 8 general medicine facilities in North-Rhine Westphalia

RaPHaeL

Research network of 60 GP practices in the states of Saxony and Saxony-Anhalt

RESPoNsE

Research network of 500 GP practices in Berlin, Brandenburg and Thuringia

1999

2012

2020

Netzwerk der Koordinierungszentren für Klinische Studien (KKSN)

German hub of ECRIN: 27 member centres

The KKSN structure enables close collaboration between study centres in multicenter trials, facilitating a high level of quality

BayFoNet

A merger of five Bavarian institutes for general medicine and 240 GP practices

FoPraNet BW

Research network 150 participating research practices in Tübingen, Heidelberg und Freiburg

SaxoForN

Research network of 50 practices in Saxony, while the existing network in the region of Frankfurt am Main (ForN) is being expanded to include a total of 200 practices

Sources: Competence Network; German Cancer Consortium; BMBF funding measure; FoPraNet BW; NRW-GPRN; RESPoNsE; SaxoForN; N.B. Not intended to be exhaustive

Clinical research networks in the United Kingdom

Most CRNs in the UK are members of the umbrella organisation UKCRN, established in 2004. In England, Wales and Ireland the main networks are broad, whereas Scotland has dedicated subject area CRNs

Scottish Primary Care Research Network
Facilitate high quality research studies, both academic and commercial

2002

Scotland Cancer Research Network
This network has more than doubled patient recruitment to Scottish clinical research studies in cancer

2003

UK Clinical Research Network (UKCRN)
Provides strategic oversight for clinical research networks across the UK to work together in an integrated manner

It includes the main UK research funding bodies; academia; the NHS; regulatory bodies; the bioscience, healthcare and pharmaceutical industries; and patients

2004

NHS NRS Children's Research Network
Supporting clinical research to improve the safety and efficacy of children's medicines and healthcare

Scottish Diabetes Research Network
Commissioned to improve the quality and increase the quantity of diabetes research in Scotland

2006

Scottish Stroke Research Network
Portfolio spans a broad range of high quality academic and commercial research activity covering cerebrovascular disease

NIHR Clinical Research Network
Comprised of 15 local CRNs and 30 specialties who support the delivery of high-quality research

2008

Scottish Neuroprogressive & Dementia Network
Promotes high-quality research into the causes, treatment and effects of dementia and other neuroprogressive diseases

Northern Ireland Clinical Research Network
Established under the UK government's health research strategy: *Best Research for Best Health*

Acts as the dedicated regional hub for advancing healthcare via clinical trials and other high-quality research across the NI health and social care environment including primary care

2009

Health and Care Research Wales
Supported by Welsh Government, which brings together a wide range of partners across the NHS in Wales, local authorities, universities, research institutions, third sector and others

Scottish Mental Health Research Network
Aims to increase the number of people participating in Mental Health research studies in Scotland

Sources: SDRN; iCAN ScotCRN; NICRN; NHS Scotland - Mental Health; Health & Care Research Wales; UKCRN; Scotland CRN ;N.B. Not intended to be exhaustive

Biobanks in The Netherlands

Despite efforts of several Dutch organisations to harmonise processes, there are still difficulties accessing samples from non-collaborative biobanks

Number of biobanks

99, dominated by UMCs and NKI

Ease of access

All focus groups mentioned problems with **FAIR**ness (Findable, Accessible, Interoperable, and Reusable)

Despite availability of samples and data, it has been reported that some biobanks are not open to sharing or collaborating. (Van der Stijl, 2019)

Consent

When patients do not explicitly object, residual material can be used for scientific research

Standardisation

The Biobank landscape in the Netherlands is fragmented despite harmonisation efforts by organisations like BBMRI-NL and Parelsnoer

One underlying cause is the competition between individual university medical centers, which limits the potential impact of biobanks for research and health care

Key Biobanks	Description
The Biobanking and Biomolecular Resources Research Infrastructure-BBMRI-NL	• Dutch node of the European research infrastructure for biobanking, BBMRI-ERIC BBMRI-NL created: - a combined **BBMRI-Omics** dataset of 3,500 samples from 29 Dutch biobanks - The **BBMRI-NL Catalogue**; collections of samples, data, and biobanks in the Netherlands - the extensive Rainbow Project "**Genome of the Netherlands**"
Health-RI	• A public-private partnership of organisations involved in health research and care • Aiming to build an **integrated health data research infrastructure** accessible for researchers, citizens and care providers
Netherlands Cancer Institute (NKI)	• The Core Facility Molecular Pathology & Biobanking registers, evaluates, and facilitates **research involving human biospecimens** (e.g., serum, blood, ctDNA, FFPE and FF biopsies, DNA & RNA)
Parelsnoer	• A **joint initiative between 8 UMCs** to provide a unified infrastructure and standardized procedures for researchers and to expand, and improve biobanks for collaborative research purposes
PALGA	• A nationwide network and **registry of histo- and cytopathology** in the Netherlands • Dutch National TissueArchive Portal (DNTP) was added to procure countrywide de-centrally located Formalin-Fixed Paraffin-Embedded (FFPE) material archives • Implementation of the DNTP improved the frequency, efficiency, and transparency of FFPE sample procurement

Sources: Please see notes

Biobanks in Belgium

Biobanks in Belgium, similarly to those of the Netherlands, operate heterogeneously, which creates difficulties in standardising quality and confidentiality

Number of biobanks

Total unspecified; 15 biobanks in BBMRI network

Landscape is dominated by University Hospitals

Ease of access

Access to samples and data remains a large challenge in Belgium

As a node of the BBMRI-ERIC, researchers that do not find suitable samples in Belgian catalogues, can be directed to the BBMRI-ERIC directory

Consent

Samples are collected under the condition of presumed consent in accordance with the Belgian law

Standardisation

The Biobank landscape in the Belgium, as in the Netherlands, is fragmented despite harmonization attempts

Individual biobanks mostly have their own rules and regulations

Operations are largely non-synergistic under the sole responsibility of the institution or hospital on which they depend

Key Biobanks	Description
BBMRI.be	• Belgian node of the European research infrastructure for biobanking, BBMRI-ERIC • The network currently connects **15 biobanks**
Belgian Virtual Tumourbank (BVT)	• **11 hospitals**, including all major university hospitals • Residual tumour tissue and related clinical data are collected by each of these sites • The BVT aims to store all this data in a centralized database
Biothèque Wallonie Bruxelles (BWB)	• An **inter-university (UCL, ULB and Ulg) collaboration** platform open to all biobanks of Brussels and Wallonia's territories
The Cardiogeneticsbank@UZA biobank	• An **academic hospital integrated biobank** with a valuable cardiogenetics collection consisting of more than 8,700 DNA samples, 380 tissue samples, and 500 cell lines of 7,578 patients
Flemish Biobank Network	• Some years ago, the funding for this initiative ended, and as a result the network is now **no longer active** • The work has mostly continued under BBMRI.be
The Inflammatory Bowel Disease Collection	• **Collaboration of three Belgian IBD centers** (University Hospitals Brussels, Ghent and Leuven) • Contains over 2.000 Crohn's disease patients, more than 700 ulcerative colitis patients, and 160 patients with Primary Sclerosing Cholangitis
VITO biobank	• This biobank, with about 70.000 biological samples from the general population in Flanders, was set up to answer research questions related to health and environment

Source: PubMed - Debucquoy 2020; Frontiers - Vande Loock; Frontiers - Cardiogeneticsbank@UZA; Biotheque-Wallonie-Bruxelles , IBD Leuven - IBD Biobank

Biobanks in Denmark

Danish biobanks are consolidated at the country-level through the Danish Biobank Register, which serves as an aggregated biobank portal for data submission and sample collection

Number of biobanks

Total unspecified ; overview is provided Danish Biobank Register, run by the Danish National Biobank

Ease of access

Sample retrieval from the Danish National Biobank requires approval from a Danish research ethics committee

Approved projects are reviewed by the DNB Evaluation Committee

In most cases a Danish non-profit collaborator is required to obtain samples

Consent

Consent varies; population-based studies broad consent vs. diagnostic samples opt-out register

Data about the donors available e.g., age, gender, and screening results are often available via Danish National Biobank

Standardisation

Most biobanks have their own operations of collections, but the Danish Biobank Register is an aggregated national collaboration containing information 27.4 million biological samples from 5.9 million Danes

Large biobanks based at hospitals, universities and other research institutions in Denmark regularly submit data to the Danish Biobank Register

Key Biobanks	Description
Bio- and Genome Bank Denmark	• **Stores biological tests** in biobank centers and in local departments • The biobank centers are responsible for managing all tests in their own region, and they make agreements with the local hospital departments that manage blood- and tissue collections
Danish Blood Donor Biobank	• Part of the Bio- and Genome Bank Denmark • Research from the Danish Blood Donor Study on why blood donors are healthier than the average population
Danish Cancer Biobank	• Part of the Bio- and Genome Bank Denmark • Blood and tissue samples from Danish cancer patients in all regions organized into six centres • The individual centers coordinate the regional biobank work, but the biobank is available through the Danish Biobank Register
Danish Diabetes Biobank	• Part of the Bio- and Genome Bank Denmark • Samples from **50,000 patients with newly diagnosed T2D**
Danish National Biobank	• **One of the world's largest biobanks** with more than 10 million samples from around 3 million individuals that can be used for research projects
Danish Rheumatological Biobank	• Established in 2015 by Arthritis Association and leading arthritis researchers Analyses are linked with the large DANBIO database • Part of the Bio- and Genome Bank Denmark
Pato Biobank	• Part of the Bio- and Genome Bank Denmark • **More than 17 million tissue samples** from national hospitals • Contains data from national pathology departments

Source: Gigtforeningen - Dansk Reuma Biobank , Patobank , Danish National Biobank , eit Health - Biobanks Denmark , PubMed - Christensen 2012

Biobanks in France

The French biobanking infrastructure is distinct in its implementation of nationwide quality management and standards of qualification, which many other countries lack

Number of biobanks

96 biological or microbiological resource centres (2021)

Ease of access

Biobanks have a prominent custodian role to the access of bioresources

Consent

Researchers must obtain informed consent from the donor of the biological material before starting any research activity

Multiple consents must be given for the process of biobanking: for storage, handling, use, and research purpose for which the participant has given their tissues and cells and associated data

Standardisation

As a centralized country, all biobanks need to be officially registered and must abide by a plethora of regulations

For a while, France was the only country with a national standard for quality management in biobanking

However, there is a push to harmonise and simplify the various informed consent processes

Key Organisations	Description
The IARC BioBank	• The IBB contains **5.1 million biological samples from 562,000 individuals** • It is one of the largest cancer biobanks in the world
BIOBank	• An independent French tissue bank for orthopaedic, spine, dental and maxillofacial surgery
Biokryo France	• In 2019 Air Liquide created a **unique biobanking network,** with biobanks in Italy, France and Germany under the BioKryo umbrella • BioKryo offers tailor-made biological **samples storage**
Infrastructures Biobanques	• Actively participates in European infrastructure BBMRI-ERIC • Structuring the network of biobanks existing on the national territory
The French Glioblastoma Biobank (FGB)	• Holds biological materials and data for **adult patients with glioblastoma from 24 centers** located throughout France
Ferdinand Cabanne Biobank Center	• The centre is actively involved in all aspects of specimen collection, preparation and preservation with a storage capacity of almost **600,000 specimens**

Source: Springer - Chassang 2021; BMC - Clavreul 2019; SagePub - Rial-Sebbag 2015; Life Sceince Europe,

Biobanks in Germany

The German Biobank Node is the central biobanking infrastructure under which the German Biobank Alliance sits; there is a national focus, as in other comparator countries, on harmonising sample access and collection

Number of biobanks

37 biobanks within the GBA

Ease of access

GBN's online 'Sample Locator' tool enables researchers to search information from multiple biobanks to locate specific samples and data

Researchers access biosamples by directly contacting a biobank location or via a mailing list

Sample distribution methods are arranged on a case-by-case basis

Consent

In German civil law, the patient can permit or refuse interactions based on general restitution norms

This applies equally to interactions with a biobank

Standardisation

GBA is pursuing a comprehensive harmonization of biobank procedures such as quality management processes and developing a linked IT infrastructure

The management of incidental research findings, however, remains an unresolved issue

Key Biobanks	Description
German Biobank Node (GBN)	• The German Biobank Node serves as a **central cooperation platform** for the German biobank community, representing their interests in the European biobank network BBMRI-ERIC
German Biobank Alliance (GBA)	• Consists of **37 academic biobank sites and one IT development centre under the GBN** • The biobanks of the GBA currently hold approximately 22 million human biosamples
BioMaterialBank Heidelberg (BMBH)	• BMBH is actively involved in the establishment of **comprehensive quality standards** within the framework of the GBA
German Cancer Research Center Heidelberg (DKFZ)	• DKFZ is the **largest biomedical research institute in Germany** • Supports the GBN with IT
Integrated Biobank Jena (IBBJ)	• The Integrated Biobank Jena is **a merger of several biobanks**
Nationale Kohorte (NaKo)	• Since 2014, the study prospectively investigates **more than 205,000 adults** • Samples and data are generated, stored and processed in each of the **18 centres**, though the main facility is the Helmholtz Centre in Munich

Source: BBMRI; Nature - Geiger 2023; Springer - Hoppe 2021; Helmholtz Munich , Biobanking - Sample Locator

Biobanks in the United Kingdom

The UKCRC Tissue Directory and Coordination Centre serves as a central inventory of sample collections, with 300 registered biobanks; however, sample accessibility remains a challenge

Number of biobanks

~300 registered resources in UKCRC TDCC

Ease of access

Despite the UK being a world leader in clinical and medical research, access to human samples is perceived to be slow, costly and lacking transparency

The most common method for current sample access is either via a local resource or self-collection

Consent

There are three main elements: general consent, ethics committee approval, and the freedom to withdraw

Consent is typically defined at the project level rather than including provisions for cross-project or subsequent re-use of samples

Standardisation

The UKCRC TDCC aims to deliver a national single-entry point for delivering access to samples by providing researchers a single access point to the UK's rich and dynamic research infrastructure

By 2030, it aims to harmonise consent, develop a single cost recovery mode, build relationships with key data partners and involve patients and public in decision-making

Key Biobanks	Description
BBMRI.uk/ UK Clinical Research Collaboration Tissue Directory and Coordination Centre (UKCRC TDCC)	• The UK Node of BBMRI, also known as the UKCRC Tissue Directory and Coordination Centre • The TDCC has developed the **UK's only register of sample collections that covers multiple diseases**
UK Biobank	• UK Biobank is a **large-scale biomedical database and research resource**, containing in-depth genetic and health information from **half a million UK participants**
The National Biosample Centre	• Established by the NIHR in 2014, and operated by UK Biocentre as a not-for-profit organisation, The National Biosample Centre provide world leading **sample management and high-capacity bioprocessing**
Human Tissue Authority (HTA)	• Created by the government, the HTA is **an independent regulator of organisations that remove, store and use human tissue** for research, medical treatment, post-mortem examination, education and training, and display in public
Northern Ireland Biobank (NIB)	• NIB is a **regional research infrastructure** creating access to biospecimens across Northern Ireland

Source: UK Biocentre, UK Biobanking Directory , UKCRC TDCC , HTA , BBMRI , Northern Ireland Biobank

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