INDUSTRY-SPONSORED CLINICAL TRIALS START-UP & RECRUITMENT PERFORMANCE METRICS

SUMMARY REPORT

IPHA

Clinical Research Exchange Group

Version 2 (updated data); November 2021

Please disregard the previous (May) version of this 2021 report[i]

I. INTRODUCTION

BACKGROUND

From an Industry perspective, a global pharmaceutical company will make their decision to sponsor an interventional drug trial in a country based on its ability to set-up in a timely manner and its ability to deliver on the patient recruitment targets that were promised.

This survey is useful to have an insight into recent performance in terms of Ireland's ability to both start-up a trial in a timely manner and to recruit patients to previously set targets.

Additionally, it is important to also understand how Ireland performs on an international level with other European countries that are comparable in terms of population and economic wealth.

This research was commissioned by the IPHA Clinical Research Exchange Group (CREG) to generate and report the evidence necessary to recommend policy-changes to improve the clinical research environment and make Ireland more attractive to future research.

OBJECTIVES

- To survey the IPHA member companies and to analyse the key performance metrics relating to trial start-up timelines, together with patient recruitment, over recent years.
- To use this survey to generate evidence to highlight issues or any roadblocks during the clinical trial process.
- To quantify and compare the number and phases of trials in Ireland relative to Denmark and Finland, from 2013 to 2020.
- To analyse what effect Covid-19 had on recruiting patients for trials in Ireland when compared to Denmark and Finland in 2020.

RESEARCH QUESTIONS

- How many calendar days has it taken to a set up a trial in Ireland over the period, from the date a company submits a trial application to a Recognised Ethics Committee (REC) to the date that a first patient is recruited?
- How many calendar days has it taken to gain Recognised Ethics Committee Approval for trials?
- How many calendar days has it taken to gain HPRA Approval from HPRA validation?
- How many patients were screened relative to the target set for each trial?
- How many patients were randomised or treated compared to the target set?
- How does Ireland compete internationally with attracting industry-sponsored clinical trials?

II. METHODS

- While the original 2021 survey request was distributed to the IPHA Membership on 23.02.21, a revised version of the survey request was distributed on 20.09.21. Members were asked to 1) verify all previous data sent to IPHA as some errors in the data sent to IPHA had been detected and 2) submit REC and HPRA application validation dates.
- For this revised Nov 2021 version, 16 responses were received between 22.09.21 and 28.10.21.
- A total of 232 trials were analysed in this Nov 2021 survey. Data was received with a 78% completion rate. Thus 22% of the data was unaccounted for. This can be viewed in Figure 18 which shows a heatmap of sample captured.
- The datasets were combined, anonymised, cleaned and enriched using Microsoft Excel.
- Calculated fields were created from the raw data submitted by respondents to enable further analysis.
- Outlier testing was performed on the combined dataset and was inspected for other anomalies, all of which were either verified, corrected, or removed through consultation with the survey respondents.
- Version 1 of this report is now withdrawn due to errors in the initial data sent to IPHA.

DATASET DESCRIPTION

IPHA Clinical Trials Survey

The primary data source used was member submitted data collected on the 2021 IPHA Clinical Trial KPIs Survey template. A list of the fields contained in the survey for data collection is provided in Figure 17.

Several calculated fields were created for measuring the trial start-up time and percentage recruitment targets achieved. This was performed by subtracting dates of interest from one another and using calendar days as the measure of time in between. Calculating the percentage of patients recruited to targets set involved dividing the target number of patients set to be screened or randomised by the number of actual patients recruited.

The key metrics reported in the survey are as follows:

Study start-up times consisting of

- Date of REC Submission to First Patient In
- Date of REC Submission to REC Approval
- Date of HPRA Validation of the submission to date of HPRA Approval
- Date of REC Approval to Contract Finalisation
- Date of Contract Finalisation to Site Green Light
- Date of Site Green Light to First Patient In

Recruitment Metrics consisting of

- % Screened Recruitment Achieved
- % Randomised Recruitment Achieved

Clinicaltrials.gov

This resource was analysed on 23.11.21 to provide meaningful international context in terms of assessing Ireland's performance in relation to attracting trials relative to its European peers. www.clinicaltrials.gov is a database of privately and publicly funded clinical trials conducted around the world and is a resource provided by the U.S Library of Medicine.

III. Results

(a) REC Submission to First Patient Screened

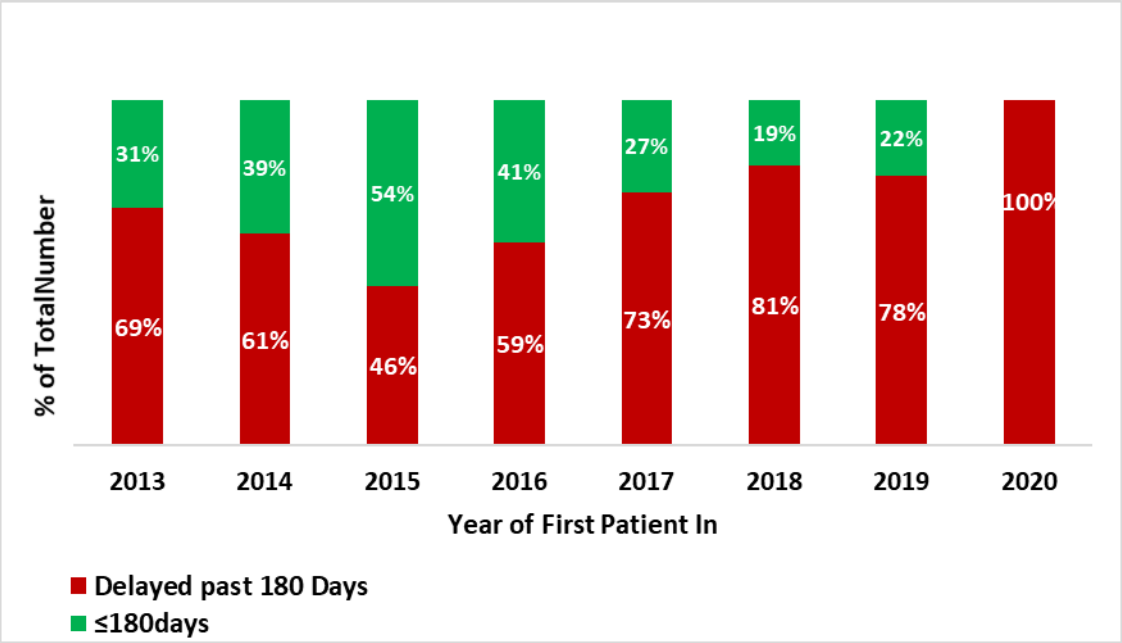
The number of calendar days between the date a company submits to a Recognised Ethics Committee and the date that a First Patient was Screened was examined for this report. This analysis covers trials where a First Patient was screened into a trial between 2013 and 2020. The minimum number of days taken to set up a trial was 83 while the maximum was 936. The median number of days taken to achieve this from the date of submission to REC was 240 days.

In 156 trials the time taken between submission of the application to the REC to first patient in was examined. For this metric 71% were delayed past 180 days, with only 29% occurring within 180 days. In 2020 (Figure 2) all trials submitted to the survey were delayed over 180 days from REC submission to First Patient Screened.

Figure 1: Number and Percentage of Trials that took over 180 days from date of submission to the REC to first patient screened, between 2013 and 2020

Over 180 Days	110	71%
Within 180 days	46	29%

Figure 2: The % Trials that took over 180 days by Year



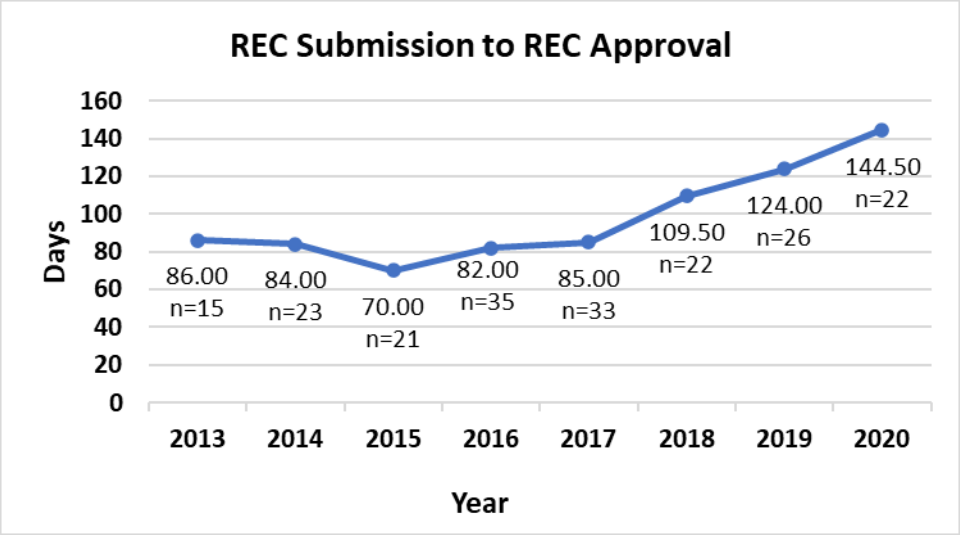
(b) REC Submission to REC Approval

The median number of days from REC submission to REC approval was 92 days (n=197), with the shortest approval time being 7 days compared to the longest being 291 days. Out of the 197 trials examined, 51% took more than 90 days compared to 49% of trials which ≤ 90 days.

Figure 3: Number & % Trials that took more than 90 days from REC Submission to REC Approval

More than 90 Days	101	51%
≤ 90 days	96	49%

Figure 4: Median Days from REC Submission to REC Approval by Year



The median number of days taken from REC submission to REC approval increased each year between 2015 and 2020. The median number of days to REC approval was 70 in 2015 rising to 144.5 in 2020.

A total of 10 trials had data on the date upon which the REC had validated the clinical trial application. For this subset the median number of days from REC validation of the application to REC approval was 71.5 days. 90% of these trials were within 90 days whereas only 40% of these trials were within 60 days. According to Irish legislation[ii], the time from receipt of a valid submission by the REC to the receipt of the opinion from that REC should be no longer than 60 days.

(c) HPRA Validation to HPRA Approval

The median number of number of days taken to approve a trial by HPRA was 57 days (n=63). The quickest approved trial was 3 days versus the lengthiest of 60 days. All 63 trials analysed in this study were approved within 60 days of validation.

Figure 5: Number & % Trials that took ≤ 60 days from HPRA validation to HPRA approval

Over 60 Days	0	0%
60 days or less	63	100%

Figure 6: Median Days from HPRA Validation to HPRA Approval

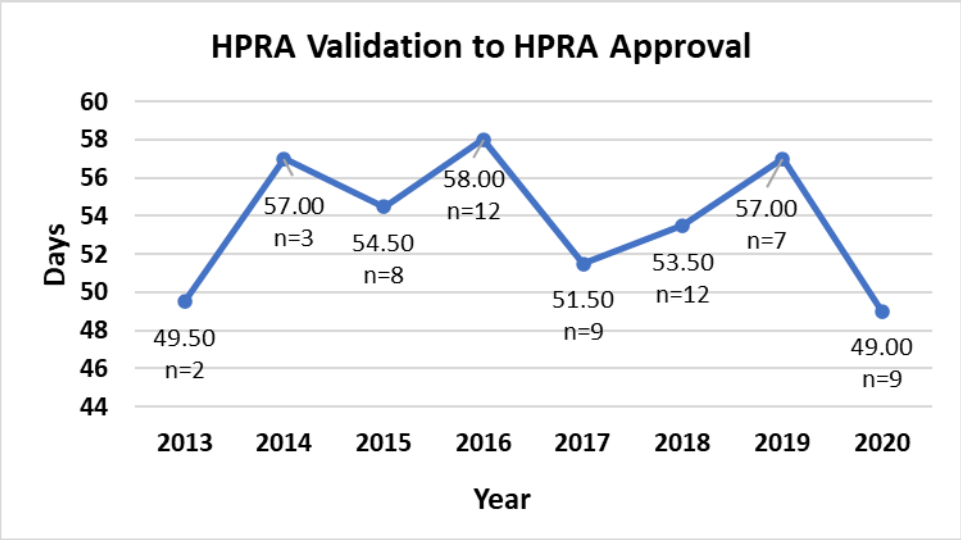


Figure 7: Descriptive Statistics for all Trial Start-up Metrics

	N	Min	Max	Mean	Median
Days from REC Submission to FPI	156	83	936	270.10	240.00
Days from REC Submission to REC Approval	197	7	291	99.84	92.00
Days from HPRA Validation to HPRA Approval	63	3	60	48.79	57.00
Days from REC Approval to Final Contract	171	-33	396	87.23	64.00
Days from Final Contract to Site Green Light	147	-5	235	39.69	25.00
Days from Site Green Light to First Patient In	136	1	466	66.91	35.00

Figure 8: Sample Spread by Trial Phase

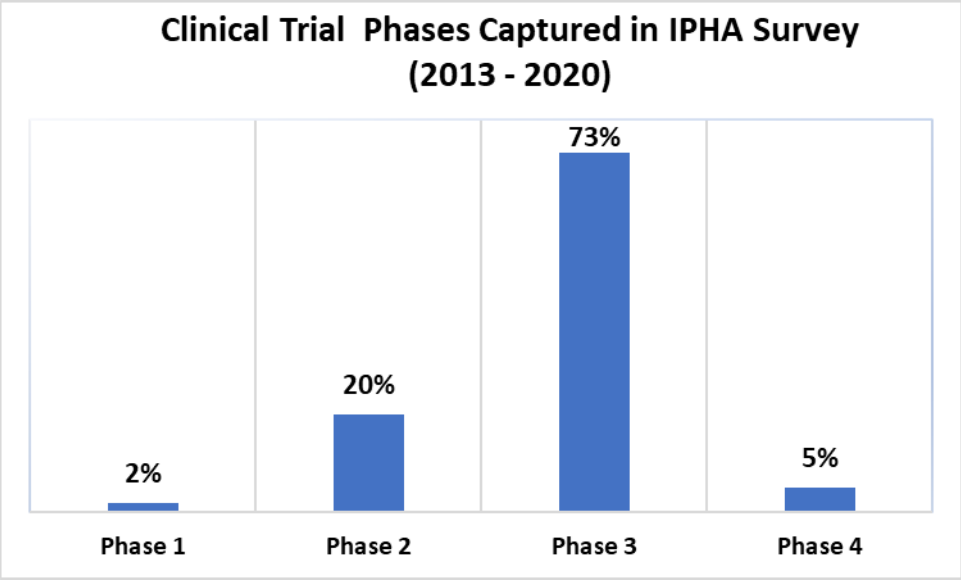
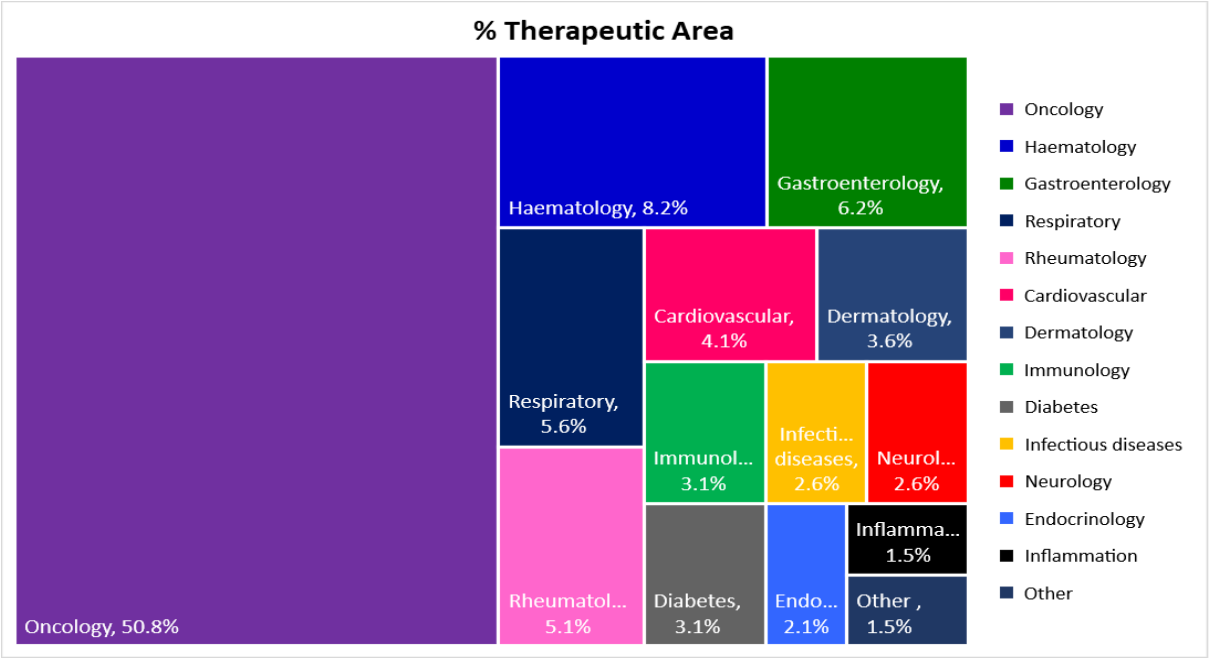


Figure 9: Sample Spread by Therapeutic Area



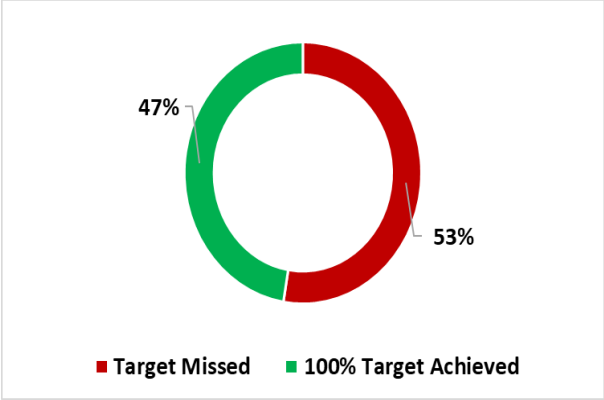
The data collected in the survey showed that the most common trials taking place in Ireland over the last 8 years (n=161), were Phase 3 trials (n=118) accounting for 73% of the trials (Figure 8). The therapeutic area leading the way in terms of clinical trials was oncology, accounting for over 50% (n=99) analysed in this study (n=195). Together, haematology (8.2%), gastroenterology (6.2%) and respiratory (5.6%) accounted for 20% of the clinical trials populated (Figure 9).

Recruitment Metrics

1. **Screened Patients**

Analysis was carried out on data received from 95 trials where the recruitment status was marked either Completed or Recruitment Closed from 2013 - 2020. In the diagram below Figure 10, the data indicates that 47% of trials achieved their 100% target for screening patients. Therefore, 53% of trials taking place from 2013 – 2020 failed to hit their screening targets. Furthermore, 60% of trials achieved a 75% target success rate while 13% of trials failed to reach 25% of their screened targets.

Figure 10: Screen Target v Actual Patients Screened

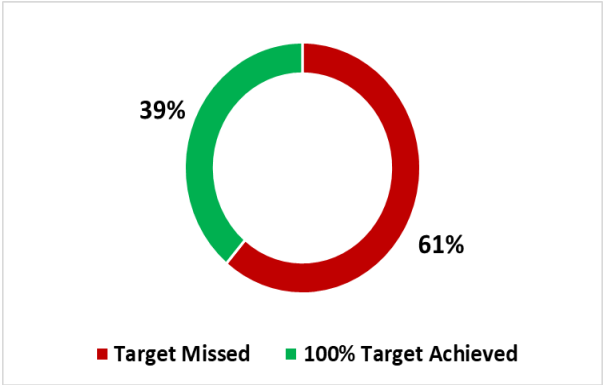


Target Missed	50	53%
100% Target Achieved	45	47%
75% Target Achieved	57	60%
Target below 25% Achieved	12	13%

2. Patients who were Randomised and then Treated

Analysis was performed on data from 116 trials received where the patients who were planned to be Randomised and then Treated (i.e., the Randomised Treatment Target) was compared to how many patients actually were randomised and treated from 2013 – 2020. The recruitment status was marked either Completed or Recruitment Closed. Figure 11 shows that only 39% of trials hit their target, with 61% of trials missing their target. Additionally, 61% of trials achieved a 75% target success rate while 19% of trials failed to even reach 25% of their target.

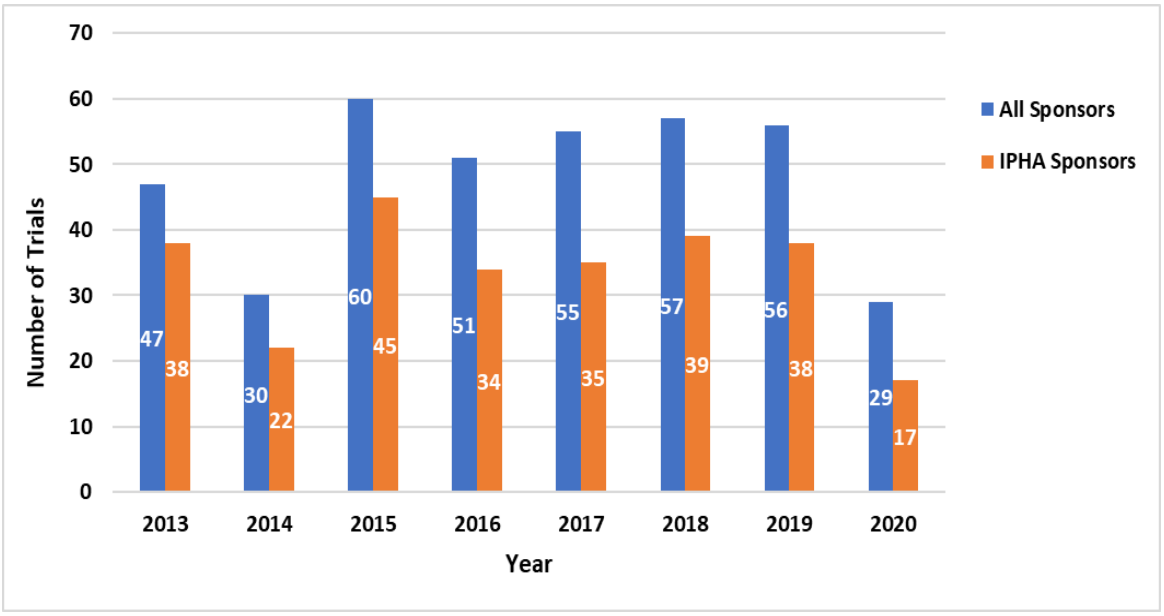
Figure 11: Randomised Treated Target v Patients Randomised Treated



Target Missed	71	61%
100% Target Achieved	45	39%
75% Target Achieved	71	61%
Target below 25% Achieved	22	19%

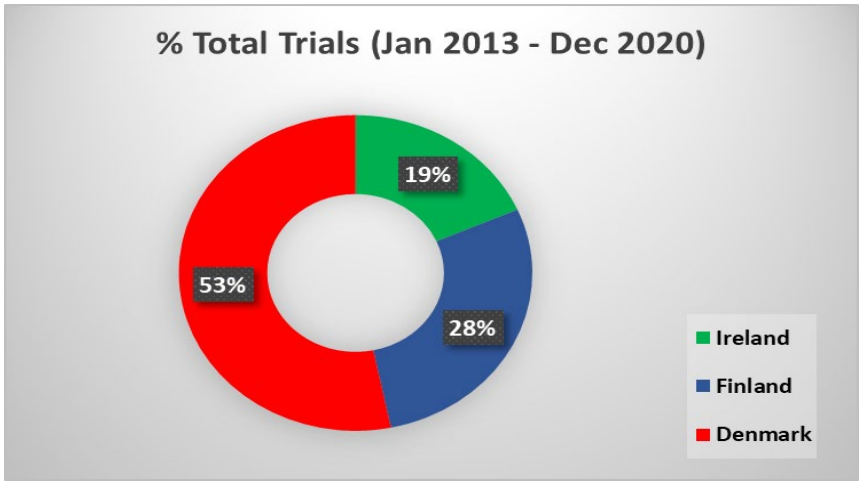
IPHA member companies performed the majority of Industry-sponsored interventional clinical trials over the period from 2013 to 2020 as calculated by the number of listed trials in clinicaltrials.gov. IPHA member company sponsored trials over this period accounted for 70% (n=268) out of 385 listed industry-sponsored trials. Figure 12 illustrates the breakdown by year of IPHA member company sponsored trials in comparison to Total Industry-Sponsored trials.

Figure 12: IPHA Sponsored Trials in comparison to Total Industry-Sponsored Trials (Source: Clinicaltrials.gov)



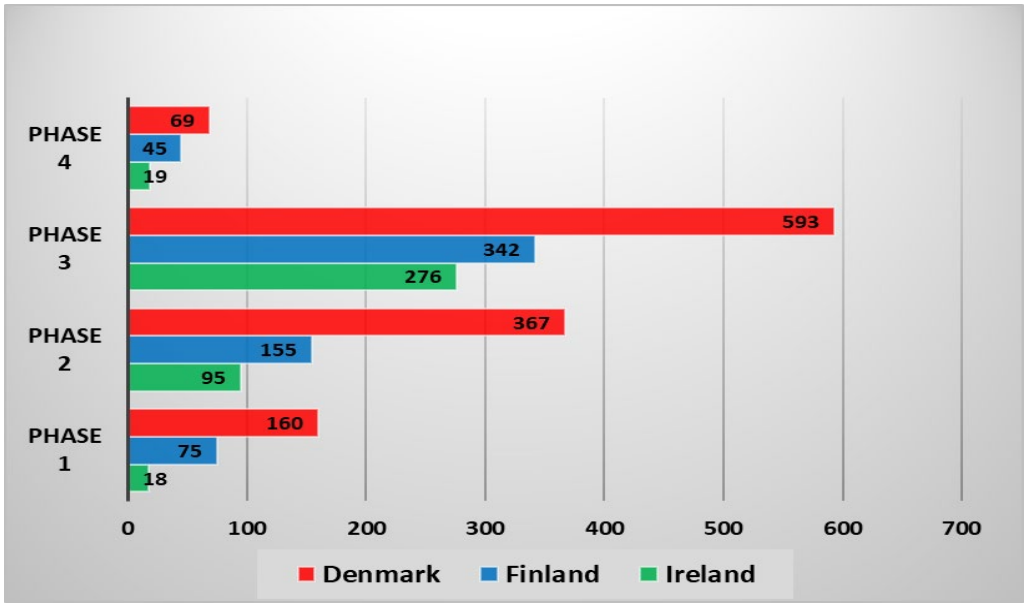
International Context

Figure 13: Number of Trials by country between 01/01/2013 and 31/12/2020 (Source: Clinicaltrials.gov)



As can be seen in Figure 13, Ireland has attracted fewer Industry-Sponsored trials than both Finland and Denmark over the period between 2013 and 2020, despite all three countries having a very similar population size and economic wealth. Ireland had 19% (n=385) of trials when compared to Denmark's 53% (n=1093) during this timeframe. The search criteria consisted of applying filters for Interventional Trials, along with the recruitment status marked as Active, Recruiting and Complete. The bar chart below in Figure 14 has trials filtered into their certain phase (Phase 1 to Phase 4). Please note that the total number of trials separated into phases for each country will be greater than the overall total for each country due to some Phase1/2 and Phase 2/3 trials added to both phases.

Figure 14: Phases of Trials identified by country between 01/01/2013 and 31/12/2021 (Source: Clinicaltrials.gov)



The line graph in Figure 15 shows a decline in trials for all three countries from 2019 to 2020 which can be accounted for due to COVID-19. However, Industry-Sponsored trials decreased by 11% in Denmark and 19% in Finland in comparison to a decrease of 48% in Ireland. This information was filtered using the recruitment status marked either Recruiting, Active or Completed.

Figure 15: Number of Trials year on year identified by country 2013-2020 (Source: Clinicaltrials.gov)

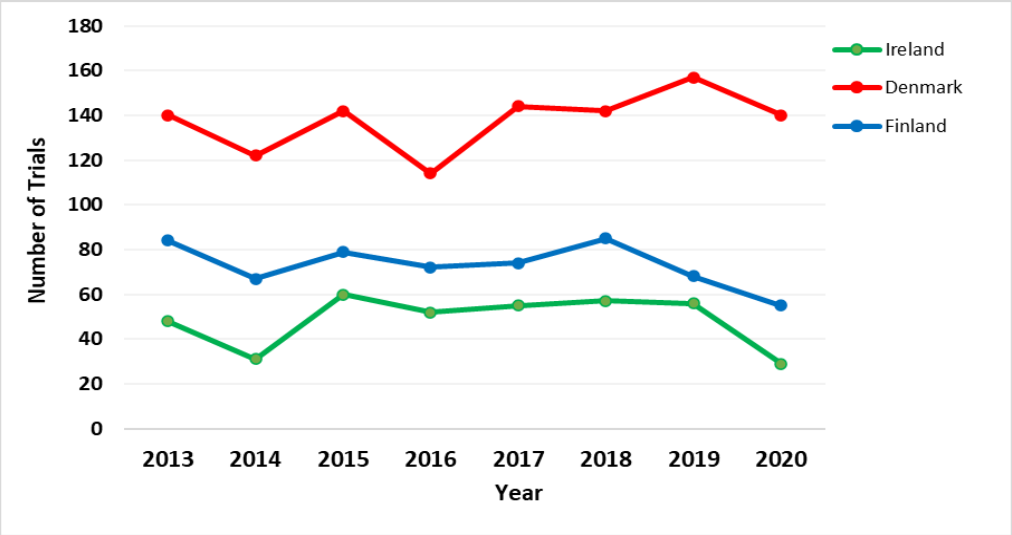
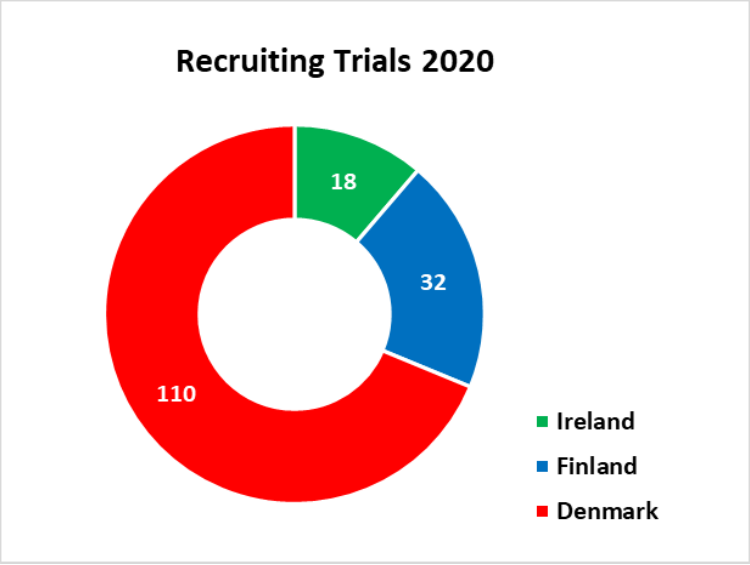


Figure 16: Total Trials Recruiting in 2020 identified by country



This information was obtained using clinicaltrials.gov and filtered for recruitment status marked Recruiting from 2020 to 2021. Again, it is evident how Ireland is lagging behind Finland and Denmark when trying to recruit Industry-Sponsored trials. Of all trials recruiting in 2020 in these three countries, Ireland only had 11% of the total. That number was 69% in Denmark.

IV. Conclusion

This survey provides clear evidence of the issues and roadblocks experienced during the clinical trial process in Ireland. Certain aspects of the process continue to cause harmful delays to the conduct of effective clinical trials here. To become internationally competitive, improve patient outcomes and ensure future investment in clinical trials in Ireland, it would be essential that the issues and roadblocks are addressed and removed.

To address this IPHA proposes that the following actions should be taken:

- Implement protected research time for clinicians and hospital staff.
- Require that hospital sites adhere to patient recruitment commitments.
- Set standard national approaches and provide clear guidance on data regulation issues.
- Standardise processes for all RECs, with no specific requirements at individual REC level.
- Improve Recognised Ethics Committee (REC) review and approval timelines.
- Demand consistency in the approach to clinical research across all institutions.
- Implement electronic patient records across all hospitals.
- Facilitate the sharing of best practice across hospital sites.

Ireland can have a lead role for clinical trials in Europe. We have a strong base of international biopharmaceutical companies, alongside global clinical leaders, together with a willing and adaptive policymaker community. Reforms are needed in the clinical trials process and, if we get them right, more patients will benefit from breakthrough medicines innovation. The search for a COVID-19 vaccine has shown how important clinical trials are in medicines' development. With the right reforms, Ireland can be a European leader in clinical trials.

Ireland is a hub for biological medicines manufacturing. We can be a leader in clinical research, too. More enrolled patients mean more clinical trials, which will ultimately benefit patient health.

Figure 17: IPHA Clinical Trial KPIs Survey Design – Field Description

Column Count	Column Letter	Data Field	Field Description	Valid Data Type accepted	Options / Used for
1	B	Company Study Identifier	Enter the Study ID used within your company database which tracks the trial	Free text	
2	C	Eudra CT Number	Enter the EudraCT number for the trial, which uniquely identifies the trial in the EU Clinical Trials register. Eg. "2012-002053-29"	Free text	
3	D	US National Clinical Trial (NCT) Number	Enter the 8 digit US NCT Number that uniquely identifies the trial on clinicaltrials.gov. eg NCT18765435	Free text	
4	E	Therapeutic Area	Enter the Therapeutic Area in which the IMP/Medicine is being studied? Select "Other Business" if Therapeutic Area Not Available	Select from drop down list	* See Glossary
5	F	Trial Phase	Enter the Phase of the Trial	Select from drop down list	Early Phase 1 (Phase 0); Phase 1; Phase 2; Phase 3; Phase 4; *Not applicable
6	G	Recruitment Status	Enter the current recruitment status of the trial (as at date of submission to IPHA) (Please refer to Glossary attached if you are uncertain as to which Status is applicable)	Select from drop-down list	Completed; Not yet initiated; Recruiting; Recruitment Closed; Suspended; Terminated; Withdrawn; Unknown status
7	H	Managed by	Enter whether the trial was managed by an in-house team or by a CRO	Select from drop-down list	In-house; CRO; Other
8	I	Date of study submission package release from Global Regulatory Affairs (or equivalent funcion)	Enter the date when the documentation required for submission to Ethics Committee/HPRA was received at the local function	dd/mm/yyyy	For Study Start-Up Timeline Metrics
9	J	Validation date of the (REC) submission	Official validation date of the submission	dd/mm/yyyy	
10	K	Date of Submisson to Irish Recognised Ethics Committee (REC)	Enter the date of submission to Irish Recognised Ethics Committee (REC)	dd/mm/yyyy	
11	L	Date of approval from Irish Recognised Ethics Committee (REC)	Enter date of letter of approval from Irish Recognised Ethics Committee (REC)	dd/mm/yyyy	
12	M	Date of Submission to HPRA	Enter the date of submission to HPRA	dd/mm/yyyy	
13	N	Validation date of the HPRA submission	Official validation date of the submission	dd/mm/yyyy	
14	O	Date of HPRA Initial / Conditional Approval	Enter date of letter of HPRA initial/ conditional approval	dd/mm/yyyy	
15	P	Date of HPRA Final Approval of the initial	Enter date of letter of HPRA final approval of the initial submission (if different from above)	dd/mm/yyyy	
16	Q	Date of final Signature on First site contract	Enter date of final signature on the first Irish Site contract to be completed	dd/mm/yyyy	
17	R	Date of Green Light Package / Site Readiness Confirmed	Enter date of 'green light' confirmation; first Irish site confirmed ready for IMP released	dd/mm/yyyy	
18	S	Date of Irish First Patient Screened	Enter date of first patient screened into the study	dd/mm/yyyy	
19	T	Date of Last Patient First Visit	Enter date (planned or actual) of last patient first visit	dd/mm/yyyy	
20	U	Total IRL *Screened* Target	Enter target set for number of screened Irish patients	whole number	% Screened Recruitment Achieved
21	V	Actual Number of IRL Patients *Screened*	Enter actual number of screened Irish patients	whole number	
22	W	Total IRL *Randomised* /Treated Target	Enter target set for total number of randomised / treated Irish patients	whole number	% Randomised Recruitment Achieved
23	X	Actual Number of IRL Patients *Randomised* / Treated	Enter actual number of randomised / treated Irish patients	whole number	
24	Y	Number of IRL sites who achieved set Randomised Target	Total Number of Irish sites to achieve set randomised / treated patient target	whole number	% Sites that Achieved Set Recruitment Target
25	Z	Total Number of IRL Sites	Enter total number of Irish sites initiated / to be initiated	whole number	
26	AA	Extra Comments (if required)	Enter any further details IF you deem it relevant or necessary	Free text	

Figure 18: Heatmap of Captured Sample Data, red indicating 22% missing values for trials (2013 – 2020)

[i] It was determined that some of the data sent to IPHA and used in the May 2021 report was erroneous. Therefore, the original 2021 report should be disregarded. This Nov 2021 report contains updated corrected data.

[ii] Reg 13(1) of SI 190 of 2004 states that an EC shall within the specified period following receipt of a valid application, give an opinion in relation to the clinical trial to which the application relates. For standard trials that period is 60 days.

Irish Pharmaceutical Healthcare Association

Making Ireland a European Leader in Clinical Research

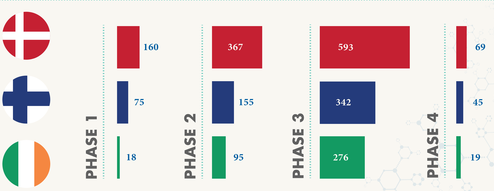
Reforms in clinical research can help accelerate medicines development.

- Implement protected research time for clinicians and hospital staff.
- Require that hospital sites adhere to patient recruitment commitments.
- Set standard national approaches and provide clear guidance on data regulation issues.
- Standardise processes for all RECs, with no specific requirements at individual RECs.
- Improve Recognised Ethics Committee (REC) review and approval timelines.
- Demand consistency in the approach to clinical research across all institutions.
- Implement electronic patient records across all hospitals.
- Facilitate sharing best practice across hospital sites.

	Ireland	Denmark	Finland
Population[1]	5.0m	5.8m	5.5m
GNI per capita[2]	US$64,150	US$63,070	US$49,700

More companies choose Denmark and Finland over Ireland to conduct clinical research.

Number of Industry-Sponsored Clinical Trials by Trial Phase and Country (2013-2020)[3]



Between 2013 and 2020, Ireland conducted 385 clinical trials across four phases. In Denmark, the number was 1093. Finland recorded 581 clinical trials. [3*]

The average wait time to recruit a patient on a clinical trial in Ireland, is 270 days.[4]

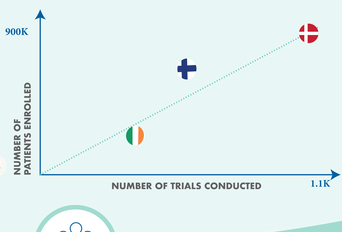
We often experience trial start-up delays and we don't always meet recruitment commitments.

Ireland can have a lead role for clinical trials in Europe.

We have a strong base of international biopharmaceutical companies, alongside global clinical leaders, and a willing and adaptive policymaker community.

Reforms are needed in the clinical trials process - and, if we get them right, more patients will benefit from breakthrough medicines innovation.

The search for a COVID-19 vaccine has shown how important clinical trials are in medicines' development. With the right reforms, Ireland can be a European leader in clinical trials.



More enrolled patients means more clinical trials. Ireland is a hub for biological medicines manufacturing. We can be a leader in clinical research, too. Let's all work together for patients.

DATA SOURCES

1: eurostat

2: THE WORLD BANK | data.worldbank.org 2020

3: U.S. National Library of Medicine ClinicalTrials.gov
(3*) Please note that the total number of trials separated into phases for each country will be greater than the overall total for each country due to some Phase1/2 and Phase 2/3 trials added to both phases. Analysis took place on 25.11.21.

4: Irish Pharmaceutical Healthcare Association | 2021 IPHA Clinical Research Survey

#InnovateForLife