DKM ECONOMIC CONSULTANTS

Health & Economic Impacts of Cancer Trials in Ireland

Final Report for Cancer Trials Ireland

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cancer trials ireland

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PREAMBLE

In 2016 Cancer Trials Ireland commissioned DKM Economic Consultants to address the following questions:

How does the work of Cancer Trials Ireland in cancer trials contribute to the wellness and survival of Irish Cancer Patients?

and

How does cancer trial activity impact the Irish Economy through job creation, income and Exchequer revenue generation, and cost (drug) savings to the HSE?

This report seeks to quantify and value the health and economic benefits of cancer trial activity in Ireland. Only the impacts in the Republic of Ireland are considered. The findings of our analysis are summarised in the Executive Summary.

KEY FINDINGS

- Of the projected €7.5 million income generated by Cancer Trials Ireland in 2016, the Exchequer (in the form of the HRB), is contributing €3.04 million.

- Grant aid provides the resources to put in place the infrastructure, and meet HPRA regulatory requirements, which enables the hospital sites to compete for the commercial/international trials and related funding.

- One of the cancer centre hospitals has provided data which points to an approximately 3:1 ratio of industry funding to grant income (HRB etc.) in 2015. In other words, for every €1 in grant funding, this hospital has succeeded in generating a further €3 in income from industry for trials. Other hospitals have pointed to similar ratios in funding.

- We estimate conservatively that drugs savings to the HSE directly from cancer trial activity is in the region of €6.5 million annually. This excludes the costs of experimental drugs, avoided treatment costs (as in the case of the Oncotype DX test), and the benefits of improved health and longer lives for patients, leading to lower future healthcare costs.

- Almost 200 people are directly employed working on cancer trials in Ireland. These are funded from a number of sources, including grants and the pharmaceutical industry. Taking into account supply chain and other multipliers, this number rises to over 230.

- This activity is estimated to add a total of €16.5 million to Irish GDP per annum, and to generate tax revenues for the Exchequer of €5.8 million per annum.

- Based on a small sample of case studies, we estimate that the health benefits of each trial (considering only the Irish patients who participated in the trials, for the period of follow-up), ranged from 6 to 16 added quality-adjusted years of life (QALYs) per trial. The related economic benefits ranged from €0.28 to €0.72 million per trial. Subsequent benefits, when therapies become available to the generality of patients, would be a multiple of these values.

EXECUTIVE SUMMARY

Cancer Trial Activity in Ireland

To date, Cancer Trials Ireland has opened over 350 cancer trials, involving more than 15,000 cancer patients in Ireland. As of December 2015 research centres around the country were working on 154 trials, 66 actively recruiting patients at that point with a further 88 in the follow-up stage.

During 2015, 2,151 patients were accrued (or recruited) to trials sponsored by Cancer Trials Ireland, pharmaceutical companies and other organisations. A further 4,576 patients were on follow-up trials, i.e. still on a trial having been accrued in previous years, to give a total of 6,727.

Patient accrual to trials has grown strongly over the last decade, from 1,376 in 2007 to 2,151 in 2015, a more than 50% increase over the period, across eight cancer centre hospitals and a further six network hospitals.

Health & Related Economic Benefits of Cancer Trials

Attributing health benefits and related economic values to cancer trials is not straightforward. We have looked at a number of case studies of completed trials and estimated that the quality adjusted years of life (QALYs) added in the follow-up period, *considering only the Irish patients who participated in the trials*, range from 6 to 16 years, with a related economic benefit of €0.28 – €0.72 million. Since these values relate to the benefits for the trial participants alone, and it is not possible at this point to quantify improved survival post the study period, they can be seen as minimal estimates of the actual benefits to Irish patients.

While not all trials might generate such success, when one considers the large number of cancer trials undertaken in Ireland since Cancer Trials Ireland was established, the benefits are likely to be very large indeed.

Furthermore, if Irish participation in these trials reduced, even modestly, the time it took these therapies to become available to the generality of Irish patients, the health and economic benefits would be very substantial. It is noteworthy that Ireland was the first country in Europe to reimburse the Oncotype DX test, which was the subject of the TAILORx trial referred to above, and one where Irish sites had a high level of participation.

Published data indicates that if Ireland's participation in the trial brought forward the availability of the Oncotype DX test in Ireland by one year, this would translate to additional QALYs of 24, with an economic value of €1.06 million. In addition, the HSE would have saved some €0.56 million in avoided healthcare costs.

Funding of Cancer Trials in Ireland

Cancer Trials Ireland's expenditure in 2016 is projected to total approximately €7.5 million, funded by a combination of grants (mainly from the HRB and the Irish Cancer Society) and other income (mainly pharmaceutical industry funding).

Cancer Trials Ireland's Group Central Office (GCO) activity level has grown very significantly over the last decade (revenues more than trebling), and the bulk of this growth has been financed by sources other than grants. In 2006 grants represented 64% of total income, while for 2016 they are projected to represent 42%.

In addition, Cancer Trials Ireland disburses HRB and pharmaceutical industry funding for clinical trials in hospitals around the country. These are projected to amount to €2.4 million and €1.8 million respectively in 2016.

Exchequer funding of Cancer Trials Ireland and the hospital sites involved in trials enables these to leverage greater funding from the pharmaceutical industry and other international funders. These trials and projects are subject to international competition, and participation requires the investment of resources in advance:

- In 2015, some 55% of Cancer Trials Ireland GCO's income came from industry, compared to 45% grants from the HRB and other sources. In 2016 this ratio is estimated to be 62:38.
- One of the cancer centre hospitals has provided data which points to an approximately 3:1 ratio of industry funding to grant income (HRB etc.) in 2015. In other words, for every €1 in grant funding, this hospital has succeeded in generating a further €3 in income from industry for trials. Other hospitals have pointed to similar ratios in funding.
- A recent project aided under the EU Commission 7th Framework Programme in the oncology field has earned its Irish partners (Cancer Trials Ireland among them) over €3.4 million.

Overall HRB funding of cancer trials has been on a downward trend over the last decade, albeit it was kept constant between 2009 and 2012, and again between 2013 and 2015. The peak year for HRB funding was 2008, at just under €4.5 million; by 2016, total funding will have fallen to €3.04 million, down one-third from the peak.

Irish Cancer Society funding of Cancer Trials Ireland has been on an upward trend over the last decade, although it is expected to fall by 10% in 2016.

Given the increase in patient participation in trials over the period, the equivalent level of grant funding per patient accrued to cancer trials in Ireland has fallen by 45% over the last decade, from a peak of €3,650 in 2009 to €2,020 in 2015. A significant further reduction can be expected in 2016, given the cut in grant income this year.

Financial Benefits of Cancer Trials to the Exchequer

Based primarily on savings from drugs supplied by the pharmaceutical companies (excluding drugs not on the market), we estimate that savings to the HSE from cancer trial activity is approximately €6.5 million per annum, significantly greater than the public funding of these trials.

Savings can also be generated via more effective treatment, directly as in the case of avoided chemotherapy as a result of the TAILORx trial, and indirectly as cancer patients enjoy better health outcomes and longer lives thus reducing the financial costs to the health services of ongoing treatment.

Economic Impacts of Trial Activity

Almost 200 people are directly employed on cancer trials in Ireland; including multiplier effects throughout the economy this rises to over 230.

We estimate that the direct impact on Irish GDP is over €10 million per annum, and including multiplier effects is over €16.5 million per annum.

The related Exchequer revenues in the form of taxes are estimated to sum to €5.8 million per annum. Again, this is significantly greater than the level of public funding of trials.

Qualitative Considerations

There are a number of factors that should be considered in the context of future public funding of cancer trials in Ireland going forward, including:

- It is projected the incidence of cancer will double in Ireland between 2015 and 2040. In this context, the *Department of Health Statement of Strategy 2015 – 2017* states:
  "With cancer incidence projected to double by 2040, the growth in demand for cancer services will continue to increase, particularly in view of an ageing population. A key task in the coming years will be to work to prevent cancer occurring in the first place as far as possible and to tackle cancer early when it does occur. That is why we are developing a third cancer strategy, for publication in 2016, which will provide the focus for cancer control for the next decade."
  Cancer trials clearly have an important role to play in cancer prevention and control.

- Relatedly, the upcoming National Cancer Strategy is expected to set a target of 5% of new patients on clinical trials, compared to 2-3% currently accrued.

- A strong cancer trial environment is attractive for oncology consultants, many of whom are US-trained, as well as for other HSE staff, as it enables them to keep abreast of and contribute to the latest developments in their respective fields. This in turn generates benefits for their patients and the wider health service.

- Ireland is a leading location for the international pharmaceuticals sector, with most of the leading global firms operating here. Many are producing or planning to produce oncology therapies, and are active in sponsoring clinical trials. These operations represent major investment in the Irish economy – one plant alone is expected to involve €900 million in investment. A strong clinical trial infrastructure is seen as a contributory factor in aiding IDA Ireland to win these projects for Ireland.

- While reduction in grant funding may not directly affect the level of industry-sponsored trial activity by Cancer Trials Ireland, it is likely to affect the level of investigator-led/non-commercial trial activity. The latter trials can address issues which are important for national health services and policy, improving patient health and saving money, but are not necessarily commercially exploitable. Reduction in grant funding is also likely to reduce the ability of hospital sites to put the required infrastructure in place and meet HPRA regulatory requirements, to enable the site to compete for the commercial/international trials and funding.

1. INTRODUCTION

1.1 CANCER TRIALS IRELAND

Cancer Trials Ireland (formerly ICORG – the All-Ireland Cooperative Oncology Research Group) was established in 1996 by a group of Irish oncology consultants. Its aim was to create more research opportunities for patients by putting a formal structure in place to make Ireland more attractive as a cancer trial location to international cancer research groups and the pharmaceutical industry. The **mission of Cancer Trials Ireland is to foster the growth of clinical trials activity and scientific research in cancer on the island of Ireland, and in the long-term to improve survival among Irish cancer patients**.

In 2000, following the Belfast Agreement, the group expanded its membership to include Northern Ireland. Membership is open to Medical, Surgical and Radiation Oncologists, as well as Haematologists and Research Specialists (Oncology Research Nurses, Site staff and Translational Scientists). As of early 2016 Cancer Trials Ireland has over 500 members, including more than 95% of the Island's cancer treating consultants. Since incorporation Cancer Trials Ireland has opened more than 350 cancer trials for more than 15,000 cancer patients.

Since 1996 Cancer Trials Ireland has developed strong links with many leading international cancer research groups such as ECOG-ACRIN, NRG, TRIO, UNC Cancer Network and CRUK[1], as well as with pharmaceutical firms developing the most promising new cancer treatments. As a result of these relationships Irish patients are being offered cutting edge research options that previously would only have been available in the US and elsewhere in Europe. While the vast majority of sites involved in Cancer Trials Ireland studies are based in Ireland, Cancer Trials Ireland also includes overseas sites in a number of trials.

Through Cancer Trials Ireland, Irish oncology research has developed a strong international reputation. Cancer Trials Ireland is one of the few main members of ECOG outside the US. Additionally, Cancer Trials Ireland sites have been top recruiters to international studies such as Cancer Trials Ireland 06-31/ECOG TAILORx and Cancer Trials Ireland 09-01/TRIO 018 (which was a key element to the FDA fast track approval of Palbociclib). Cancer Trials Ireland now acts as European

[1] Respectively, the merged Eastern Cooperative Oncology Group (ECOG) and American College of Radiology Imaging Network (ACRIN) (http://ecog-acrin.org/); the combined National Surgical Adjuvant Breast & Bowel Project (NSABP), Radiation Therapy Oncology Group (RTOG), and Gynecologic Oncology Group (GOG) (https://www.nrgoncology.org/); Translational Research In Oncology (http://www.trioncology.org/); University of North Carolina Cancer Network (https://unclineberger.org/unccn); Cancer Research UK (http://www.cancerresearchuk.org/).

sponsor for a number of studies, for example two ANZUP[2] prostate cancer studies which are open in the UK, and EORTC[3] sites[4].

1.2 BACKGROUND TO THIS STUDY

Very significant progress has been made in the treatment of cancer in Ireland over the last two decades. In 1995 there were three oncologists working in Ireland – today there are over 30. The 2014 review of the 2006 National Cancer Strategy[5] points to substantial improvements in survival rates for many cancers over the same period.

It is also 20 years since the establishment of Cancer Trials Ireland. In view of this 20th anniversary, the purpose of this study is to measure and highlight the importance of cancer trials in Ireland, and Cancer Trials Ireland's function in organising, promoting and undertaking cancer trials. A robust level of trial activity is seen as having positive impacts in terms of:

(i) improved health outcomes for Irish cancer patients, and
(ii) economic benefits to Ireland in terms of savings to the health service in treating cancer patients, and employment opportunities.

This is a particularly important health issue for Ireland. Notwithstanding the progress made to date, the 2014 review of the 2006 Cancer Strategy indicated that there needed to be a minimum of 60 oncologists working in Ireland to match international standards – almost double the current number.

The National Cancer Control Programme (NCCP) indicates that each year in this country, approximately 28,500 people develop cancer, and over 8,000 die from the disease, making it the second most common cause of death after circulatory diseases[6]. Furthermore, the incidence of cancer is expected to grow by 25% in Ireland over the period 2010 to 2020, and is projected to double by 2040[7].

Two studies on Cancer Trials Ireland's activities have been undertaken in recent years, namely Technopolis (2012)[8], and Health Research Board (HRB) International Panel Review (2015)[9]. Both have been positive in terms of the value of Cancer Trials

[2] Australian & New Zealand Urogenital & Prostate Cancer Trials Group (https://www.anzup.org.au/default.aspx).
[3] European Organisation for Research and Treatment of Cancer (http://www.eortc.org/)
[4] http://www.Cancer Trials Ireland.ie/about-us
[5] http://health.gov.ie/wp-content/uploads/2015/05/Final-Evaluation-Panel-Report-of-National-Cancer-Strategy-2006.pdf
[6] http://www.hse.ie/eng/services/list/5/cancer/about/
[7] National Cancer Registry, 2014, *Cancer Projections for Ireland 2015-2040*, http://www.ncri.ie/sites/ncri/files/pubs/Cancer%20projections%20for%20Ireland%202015%20-%202040.pdf
[8] Technopolis, 2012, *Impact Assessment of the All-Ireland Cooperative Oncology Research Group,* report for HRB.
[9] In 2015 the HRB organised a scientific review of Cancer Trials Ireland. The Standing Panel met in April 2015 and was chaired by Professor Martin Gulliford, Kings College London. The panel assessed Cancer Trials Ireland's progress to date towards achieving its mission, fulfilling its stated purpose and achieving specific conditions of the HRB award and to make a recommendation if continued funding is justified.

Ireland's activities, and have quantified the various activities and impacts of Cancer Trials Ireland, including financial impacts, but did not fully examine the economic values of those activities:

> *"The panel viewed the review as a constructive and positive experience considering the state of evolution of ICORG and the Statistical Data Management Office (SDMO at Clinical Research Facility in Galway). The panel consider ICORG as an essential resource in cancer research to improve the effectiveness of cancer care in Ireland and therefore they recommend that ICORG and the SDMO be provided with continued funding taking into consideration the feedback and recommendations..."*
> ***HRB International Panel Review (2015)***

> *"(There is) some qualitative evidence that ICORG's comprehensive breast cancer research portfolio has helped Ireland to make full use of internationally developing treatments and diagnostics that resulted in a 10% improvement in the five-year survival rate in breast cancer."*
> ***Technopolis (2012)***

Internationally, studies have found very strong positive impacts on both the economy and health from medical research[10], but we are not aware of analysis of the impacts of cancer trials as such. As a result, in 2016 the Board of Cancer Trials Ireland appointed DKM Economic Consultants to undertake a study to quantify and value these impacts. DKM have been asked to address the following questions:

How does the work of Cancer Trials Ireland in cancer trials contribute to the wellness and survival of Irish Cancer Patients?
and
How does cancer trial activity impact the Irish Economy through job creation, income and Exchequer revenue generation, and cost (drug) savings to the HSE?

For the purposes of the current study, while Cancer Trials Ireland is an all-island initiative, the report focuses on impacts in the Republic of Ireland. For convenience, all references in this report to Ireland refer to the Republic of Ireland, unless the context indicates otherwise. Furthermore:

1. Trials sponsored by Cancer Trials Ireland and by pharmaceutical companies and other organisations are included;
2. Cancer Trials Ireland's work outside Ireland is also considered to the degree that it generates economic impacts in Ireland.

[10] For instance, a 2008 UK study for the Wellcome Trust, the Medical Research Council (MRC) and the Academy of Medical Sciences, *Medical Research: What's it worth? Estimating the Economic Benefits from Medical Research in the UK*, found very strong returns in terms of both health benefits and industrial investment leveraged, from research into cardiovascular disease and mental health. http://www.wellcome.ac.uk/stellent/groups/corporatesite/@sitestudioobjects/documents/web_document/wtx052110.pdf

The analysis has been undertaken via a combination of statistical/financial analysis and stakeholder consultations, and literature review, along with a number of case studies.

1.3 REPORT STRUCTURE

The report is laid out as follows:

Chapter	Title
2	Cancer Trial Activity in Ireland
3	Health and related Economic Benefits of Cancer Trials
4	Financial Benefits of Cancer Trials to the Exchequer
5	Economic Impacts of Cancer Trial Activity

The findings and conclusions are summarised in the Executive Summary at the start of the report.

2. CANCER TRIAL ACTIVITY IN IRELAND

2.1 TRIAL ACTIVITY DATA

Cancer Trials Ireland collects data on all cancer trials undertaken in Ireland, whether Cancer Trials Ireland-sponsored or not. Trials are categorised across a number of dimensions:

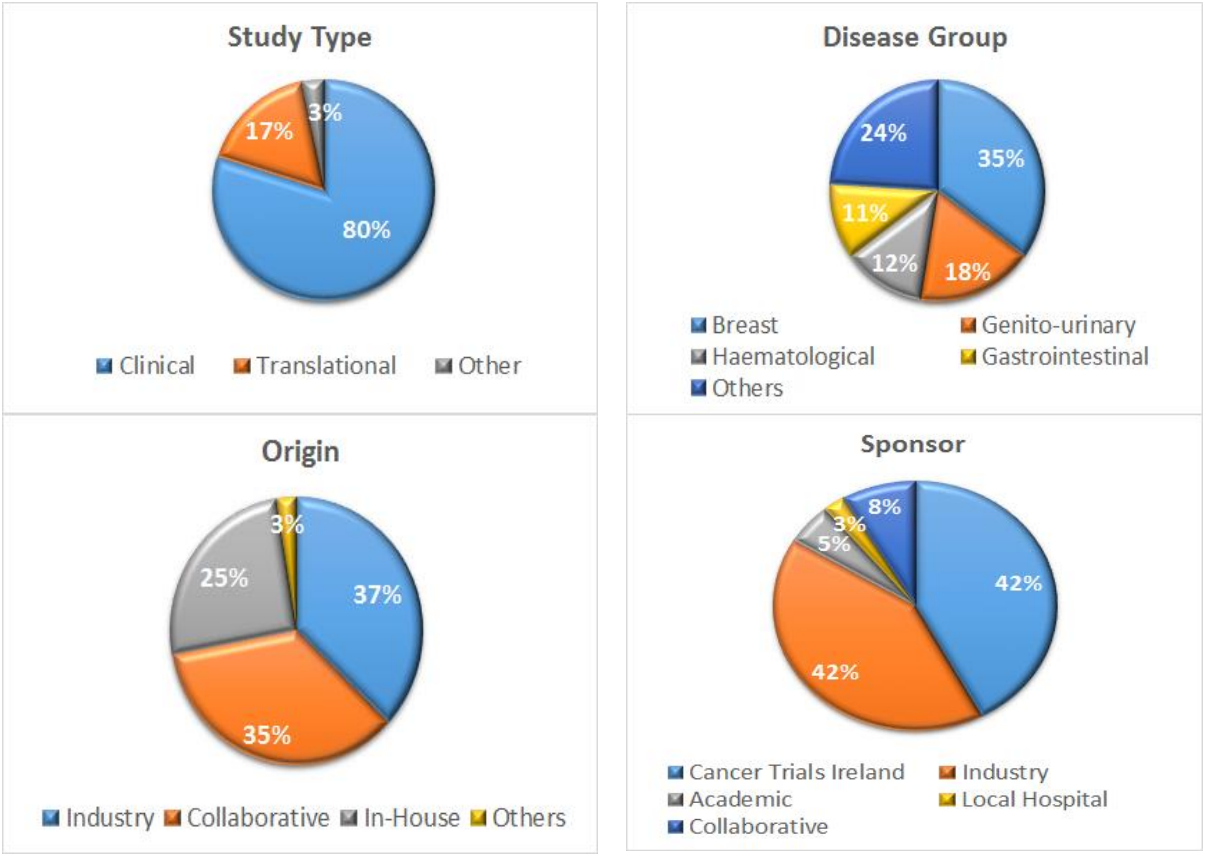
- Study **type**:
  - clinical trials, including radiotherapy trials - involving investigational medicinal products or radiotherapy or a combination of both;
  - translational studies – patients on standard non-interventional treatment, collection of biological samples for research with the aim of better understanding the drug action in the body and to find early markers for drug resistance and/or progression/recurrence of the cancer;
  - questionnaire studies;
  - other.
- Broad **disease** area: breast, central nervous system, gastrointestinal (including pancreas, liver and biliary cancer), genitourinary (including prostate and renal cancer), gynaecological, haematological malignancies, head and neck, lung, melanoma and skin cancer, paediatric, translational, other.
- Trial **origin**: industry, collaborative Group, local, other.
- Trial **sponsorship**: Cancer Trials Ireland, pharmaceutical companies, academic, local hospital site, non-commercial collaborative groups, other.
- Clinical **phase**:
  - Phase I: first in humans, to establish safe dose;
  - Phase II: effectiveness & safety in small numbers of patients;
  - Phase III: pivotal trial to establish comparative efficacy in large numbers of patients;
  - Phase IV: 'post marketing' surveillance for adverse effects, longer term morbidity & mortality.

"We're in the midst of a golden age of cancer research"
(Harpal Kumar, Chief Executive of Cancer Research UK) [11]

As indicated, to date, Cancer Trials Ireland has opened 350 cancer trials involving more than 15,000 cancer patients in Ireland. As of December 2015, Cancer Trials Ireland was working on a total of 154 studies, categorised as per Figure 2.1 overleaf.

[11] http://www.manchester.ac.uk/discover/news/article/?id=6520

Figure 2.1: CATEGORIES OF CANCER TRIALS, DECEMBER 2015



Source: Cancer Trials Ireland Activity Report 2015.

Cancer has been the most active area for clinical trials in Ireland for some years. To quote the 2014 Annual Report of the Health Products Regulatory Authority (HPRA)[13], which is responsible for authorising all interventional clinical trials of medicinal products and devices in Ireland:

"In 2014, 80 clinical trials were approved to commence in Ireland down from a total of 102 in the previous year. The key areas of interest continue to include oncology and haematology."

"Over 90% of the population acknowledged the value of conducting Cancer Research in Ireland."
Mater Hospital/IPPOSI Survey[12]

Cancer Trials Ireland indicates that over the 3-year period 2013-2015 inclusive, some 10% of Irish patients diagnosed with cancer were enrolled on a trial (3.5% drug trials and 6.5% Translational). In 2015, some 2,151 patients were accrued (or recruited) to trials sponsored by Cancer Trials Ireland, pharmaceutical companies and other organisations. Table 2.1 sets out the disease area for these accruals, while Table 2.2 sets out the trial type.

[12] Kelly, CM, 2015, *Understanding and attitudes towards cancer clinical research among breast cancer patients compared to the general population: prospective cross-sectional study.* Department of Medical Oncology, Mater Misericordiae University Hospital, Research Department & Irish Platform for Patients' Organisations, Science and Industry (IPPOSI). http://cancerres.aacrjournals.org/content/76/4_Supplement/P5-09-14.abstract?cited-by=yes&legid=canres;76/4_Supplement/P5-09-14

[13] https://www.hpra.ie/docs/default-source/publications-forms/corporate-policy-documents/hpra---press-release---2014-annual-report---2sept2015.pdf?sfvrsn=0

A further 4,576 patients were on follow-up trials, i.e. still on a trial having been accrued in previous years (excluding Belfast City Hospital). The numbers accrued to trials have been growing steadily over the last decade, as Figure 2.2 shows, from 1,376 in 2007 to 2,151 in 2015, a more than 50% increase over the period.

Table 2.1: PATIENT ACCRUALS TO CANCER TRIALS, 2015

Disease Area	Patients
Breast	1,117
CNS	61
Gastro-intestinal	158
General	161
Genito-Urinary	196
Gynaecology	18
Haematological	143
Head & Neck	6
Lung	70
Melanoma	155
Other	66
Total	**2,151**

Excludes 640 accrued patients at Belfast City Hospital.
Source: Cancer Trials Ireland Activity Report 2015.

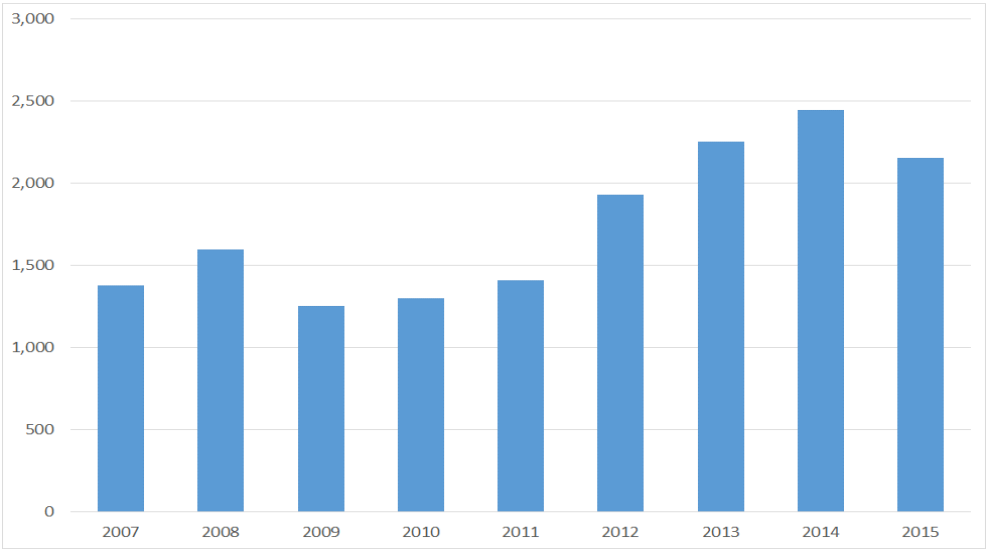
Table 2.2: PATIENT ACCRUALS BY TRIAL TYPE, 2015

Study Type	Patients	%age Split
Clinical	649	30%
Questionnaire	118	5%
Translational	1,138	53%
Other	246	11%
Total	**2,151**	**100%**

Excludes 640 accrued patients at Belfast City Hospital.
Source: Cancer Trials Ireland Activity Report 2015.

"Our patients have access to innovative drug treatments which may result in improvements to an individual person's cancer outcome and overall survival plus subsequent future patients. They may have access to new drugs/therapies or a new application for an existing drug before these are generally available or standard of care in this country."
(Oncology team, Irish hospital)

Figure 2.2: PATIENT ACCRUALS TO CANCER TRIALS IN ROI, 2007-2015



Source: Cancer Trials Ireland Annual Activity Reports.

2.2 Trial Sites & Pharmaceutical Industry

The trial sites are the hospitals that participate in the trials, whether Cancer Trials Ireland- sponsored or otherwise. These comprise the eight national cancer centres and a further six network hospitals, namely:

"By participating in cancer trials we'll bring up the standard of care across the unit."
(Oncology consultant, Irish hospital)

Cancer Centres
BH (Beaumont Hospital)
MMUH (Mater Misericordiae University Hospital)
SJH (St. James' Hospital)
SVUH (St Vincent's University Hospital)
CUH (Cork University Hospital)
UHW (University Hospital Waterford)
UHL (University Hospital Limerick)
UHG (University Hospital Galway)

Others
AMNCH (Adelaide & Meath Hospital incorporating the National Children's Hospital, Tallaght)
OLCHC (Our Lady's Children's Hospital, Crumlin)
SLRON (St. Luke's Radiation Oncology Network)
SGH (Sligo University Hospital)
LGH (Letterkenny University Hospital)
MRHT (Midland Regional Hospital (Tullamore)

A large number of the major pharmaceutical firms active in Ireland participate in cancer trials, either as sponsors or in collaborative studies, and provide significant monetary funding as well as drugs to trials. The financial and economic impacts of their activities are assessed later in this report.

3. HEALTH & RELATED ECONOMIC BENEFITS OF CANCER TRIALS

Health benefits of cancer trials arise as patients gain access to therapies that would not otherwise be available, more individualised treatment, and a better standard of care, in the sense of more intensive monitoring, testing, etc. These can lead to better health outcomes for patients, in terms of:

- Additional years of life and better quality of life;
- Shorter time in hospital and avoided treatment; and possibly
- Earlier return to the workforce.

"Trials can often offer an alternative treatment for patients that may have a rare disease with limited treatment options available to them.
In addition to their standard of care treatment, being part of a Clinical Trial means that the patient has the additional focus of a dedicated Research Nurse and Clinical Research team looking after them who monitor them more frequently."
(Oncology team, Irish hospital)

These benefits relate most directly to patients participating on the trials, but potentially also to the general body of patients in Ireland, where trials facilitate the quicker adoption of improved drugs and treatments. This can arise because, when Irish cancer centres and patients participate in a successful trial for a drug, the drug in question has a local familiarity and a readymade advocacy during the approval process.

Most trials are international and the net impact of the Irish participants to international approval of a new treatment may be relatively modest (with some exceptions such as the TAILORx trials where three of the top 15 recruitment sites were in Ireland - see Case Study 1 overleaf).

It has been well-established that the five-year relative survival rate from breast cancer has increased from 75% in the 1990s to 85% in the late 2000s. Table 2.1 meanwhile highlights the focus of cancer research in Ireland on Breast Cancer. Technopolis (2012)[14] concluded that there was "*some qualitative evidence that Cancer Trials Ireland's comprehensive breast cancer research portfolio has helped Ireland to make full use of internationally developing treatments and diagnostics that resulted in a 10% improvement in the five-year survival rate in breast cancer.*"

TAILORx

While TAILORx is perhaps the best-known of the cancer trials in which Ireland had a significant participation, it is not straightforward to attach additional years of life to it, since it removed the need for chemotherapy for the patients in question. These patients' quality of life would have been improved by virtue of avoiding chemotherapy. If we were to assume, by reference to the details of the trial set out in the box overleaf) that 15.9% of the 690 Irish women on the trial (110 patients) avoided three months of chemotherapy, that is 27 years of chemotherapy avoided. Hospital oncology staff point to a further approximately three months per patient to recover from the effects of chemotherapy.

[14] Technopolis, 2012, *Impact Assessment of the All-Ireland Cooperative Oncology Research Group,* report for HRB.

"TAILORx is one of the first and most important trials using a gene panel test to determine how to most effectively treat women with breast cancer."[15]

Case Study 1

TAILORx Trial: Program for the Assessment of Clinical Cancer Tests (PACCT-1): Trial Assigning IndividuaLized Options for Treatment

This is the first prospective evaluation of a widely used genetic test for breast cancer recurrence risk (Oncotype DX). TAILORx is perhaps the best known of the cancer-related trials that Irish hospitals and researchers have participated in, in recent years. This was an international trial led by the Eastern Co-operative Oncology Group (ECOG) in the US. The study population included patients with oestrogen-receptor (ER) positive, axillary lymph node negative breast cancer, who are suitable candidates for adjuvant chemotherapy. This is a clinical scenario in which approximately 80% of patients are "over-treated" i.e. would have been cured with hormonal therapy alone.

As reported in the *New England Journal of Medicine*† in 2015, an assay of 21 genes was performed on tumour tissue, and the results used to calculate a score indicating the risk of breast cancer recurrence. Patients were assigned to receive endocrine therapy without chemotherapy if they had a recurrence score of 0 to 10, indicating a very low risk of recurrence (on a scale of 0 to 100, with higher scores indicating a greater risk of recurrence). Among patients with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who met established guidelines for the recommendation of adjuvant chemotherapy on the basis of clinicopathologic features, those with tumours that had a favourable gene-expression profile (15.9% of trial participants) had very low rates of recurrence at five years with endocrine therapy alone, confirm that this group does not benefit from chemotherapy.

Continued follow-up and analysis in the trial is ongoing, with full results expected in several years, to determine whether adjuvant chemotherapy improves outcomes over hormone therapy alone in women with higher recurrence scores.

This study is of high health and clinical practice impact, given both the impact on patients and the cost to health systems of chemotherapy. Irish research inputs to this trial were significant:

- Total number of patients accrued in Ireland: 690.
- 30% of all eligible patients were accrued in Ireland.
- 6% of total study accrual worldwide.
- Three of the top 15 recruiting sites worldwide were in Ireland, and St Vincent's University Hospital, Dublin was the second highest recruiting site of 975 sites worldwide.

Cancer Trials Ireland was acknowledged as an author affiliation in the published journal article.

† Sparano, JA, Keane, MM *et al*., 2015, "Prospective Validation of a 21-Gene Expression Assay in Breast Cancer", *New England Journal of Medicine,* November 19, 2015 vol. 373 no. 21. http://www.nejm.org/doi/full/10.1056/NEJMoa1510764

Quality Adjusted Life Years (QALYs) are widely used to indicate quality of life with various diseases[16], with 1.0 representing perfect health and 0.0 representing death. If we were to assume that undergoing chemotherapy reduced quality of life by 0.2 QALYs during the course of treatment and the recovery period (all else equal), then

[15] Jo Anne Zujewski, MD, US National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP). http://www.cancer.gov/types/breast/research/tailorx-low-risk

[16] http://www.who.int/quantifying_ehimpacts/publications/en/9241546204chap3.pdf

the number of QALYs saved by this trial for the participants in Ireland alone was 11[17].

In economic terms, we can apply the Value of a Statistical Life (VOSL) widely used in Ireland, of €45,000 per annum[18], to this number of QALYs, to give a value of €0.5 million. Since this is the benefit for the trial participants alone, and we are not aware of improved survival rates post five years, it can be seen as a minimal estimate of the actual benefits to Irish patients.

The HSE also benefitted to the degree that the 110 patients in question avoided chemotherapy. Smyth *et al.* (2015) [19] estimate that the cost in question is approximately €7,000 per patient (ex VAT), indicating a total cost saving for the HSE of €766,000 (ex VAT).

Ireland was the first country in Europe to reimburse the OncotypeDX test (the subject of the TAILORx trial), which has provided the opportunity to avoid needless chemotherapy to the generality of Irish breast cancer patients, while also generating a financial saving to the health service. Smyth *et al.* (2015) estimate that over a 17-month period (October 2011 to February 2013) the roll-out of the OncotypeDX test:

- Enabled 335 patients to avoid chemotherapy, which converts to 34 additional QALYs, and an economic benefit of €1.5 million, equivalent to an annualised €1.06 million.
- Enabled a treatment costs saving to the HSE just under €800,000, equivalent to €560,000 per annum[20].

Thus, if Ireland's strong involvement in the TAILORx trial brought forward the availability of the OncotypeDX test in Ireland by even one year, then the economic benefit would be over €1.6 million, made up of €1.06 million in better health for the patients in question, and €560,000 in healthcare costs savings, captured by the HSE.

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

This industry-sponsored phase 3 trial, for patients with previously untreated advanced melanoma, was adopted by Cancer Trials Ireland and 27 patients were enrolled in Ireland. Assuming they were divided into the three test groups evenly and that one-third of them experienced an additional four months survival, and one third experienced 8.6 additional months survival, compared to the group treated with ipilimumab alone, then an additional 9.45 years of life would have been generated, for the patients on the trial alone. If converting this to QALYs reduced it by one-third (bearing in mind that these patients have advanced melanoma), then

[17] 690 x 15.9% x 3/12 x2 x 0.2 = 11

[18] https://www.hiqa.ie/system/files/Economic-Evaluation-Guidelines-2014.pdf

[19] Smyth, L., *et al*., 2015, "Economic impact of 21-gene recurrence score testing on early-stage breast cancer in Ireland", in *Breast Cancer Res Treat* (2015) 153:573–582. http://www.ncbi.nlm.nih.gov/pubmed/26364296

[20] Net of the cost of the Oncotype DX test, which would not have arisen during the trial period.

the additional QALYs are 6.3. At €45,000 per QALY, this generates a benefit of over €0.28 million.

Case Study 2

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

This industry-sponsored phase 3 trial was adopted by Cancer Trials Ireland and 27 patients were enrolled in Ireland. Enrolled patients were randomly assigned in a 1:1:1 ratio to receive one of the following regimens: 3 mg of nivolumab per kilogram of body weight every 2 weeks (plus ipilimumab-matched placebo); 1 mg of nivolumab per kilogram every 3 weeks plus 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses, followed by 3 mg of nivolumab per kilogram every 2 weeks for cycle 3 and beyond; or 3 mg of ipilimumab per kilogram every 3 weeks for 4 doses (plus nivolumab-matched placebo).

As reported in the *New England Journal of Medicine*†, among patients with previously untreated advanced melanoma, the trial reported longer progression-free survival and higher rates of objective response with nivolumab alone and with the combination of nivolumab and ipilimumab than with ipilimumab alone. During a follow-up period of approximately 12 months, the median progression-free survival was 6.9 months in the nivolumab group, 11.5 months in the nivolumab-plus-ipilimumab group, and 2.9 months in the ipilimumab group. The management of adverse events with the combination therapy suggests that it can be used safely in a broad range of clinical settings.

†Larkin, J., et al., 2015, "Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma", in *New England Journal of Medicine*, 2015; 373:23-34, July 2, 2015. http://www.nejm.org/doi/full/10.1056/NEJMoa1504030#t=article

Trastuzumab (Herceptin)

The adoption of Trastuzumab (Herceptin) on foot of the trials described in Case Study 3 has had a definite impact on years of additional life. Some 129 Irish patients were accrued to the trial, and the study concluded that the 5-year disease-free survival rates grew from 75% to 82.5% for the combined active groups. That implies that those Irish patients on the trial experienced an additional 16 disease-free years[21]. In economic terms, we can apply the Value of a Statistical Life (VOSL) widely used in Ireland, of €45,000 per annum[22], which translates to €0.72 million. Since this is the benefit for the trial participants alone, and we are not aware of improved survival post five years, again it can be seen as a minimal estimate of the actual benefits to Irish patients[23].

[21] 129 x 2/3 x (0.825 – 0.75) x 5 ÷ 2 = 16 (assuming disease recurrence would otherwise happen halfway through the 5-year period).

[22] https://www.hiqa.ie/system/files/Economic-Evaluation-Guidelines-2014.pdf

[23] It is worth bearing in mind also that the other patients who received active treatment would also have increased disease-free survival (they just didn't cross the 5 year threshold), so even a modest increase in disease-free survival time for these patients would translate to further QALYs and economic benefits.

"This long follow-up of patients shows that we have really altered the natural history of this disease. Herceptin works -- and it works for a long period of time. The drug has impacted the lives of many women in the U.S. and worldwide."[24]

Case Study 3

BCIRG 006: Multicenter Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide followed by Docetaxel (AC->T) with Doxorubicin and Cyclophosphamide followed by Docetaxel and Trastuzumab (AC->TH) and with Docetaxel, Carboplatin and Trastuzumab (TCH) in the Adjuvant Treatment of Node Positive and High Risk Node Negative Patients with Operable Breast Cancer Containing the HER2 Alteration.

HER2-positive breast cancers make too much of the HER2 protein. This protein sits on the surface of cancer cells and receives signals that tell the cancer to grow and spread. About one out of every four breast cancers is HER2-positive, and they tend to be more aggressive and harder to treat than HER2-negative breast cancers. Trastuzumab (Herceptin) works by attaching to the HER2 protein and blocking it from receiving growth signals†.

Trastuzumab improves survival in the adjuvant treatment of HER2-positive breast cancer, although combined therapy with anthracycline-based regimens is associated with cardiac toxicity.

This international trial of 3,222 women evaluated the efficacy and safety of a new nonanthracycline regimen with trastuzumab. Some 129 (4%) of those participating in the trial were accrued in Ireland.

The study found that addition of one year of adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer. The risk–benefit ratio favoured the nonanthracycline TCH regimen over AC-T plus trastuzumab, given its similar efficacy, fewer acute toxic effects, and lower risks of cardiotoxicity and leukaemia.

This study was practice-changing: the use of trastuzumab (Herceptin) in HER2-positive early breast cancer became standard of care in 2005 following the first release of these results. The findings were published in the *New England Journal of Medicine*†† with Cancer Trials Ireland acknowledged as an author affiliation.

† http://www.breastcancer.org/research-news/herceptin-offers-long-lasting-benefits

†† Slaman, D., Crown, J., *et al.,* 2011, "Adjuvant Trastuzumab in HER2-Positive Breast Cancer", *New England Journal of Medicine,* October 6, 2011 vol. 365 no. 14. http://www.nejm.org/doi/full/10.1056/NEJMoa0910383

NeoAEGIS: MAGIC vs. CROSS

Case Study 4 (NeoAEGIS: MAGIC vs. CROSS) is a good example of a collaborative trial led by Cancer Trials Ireland, which is not industry-sponsored but still address important clinical issues, and whose results will be valuable for patients, clinicians and public health services. It addresses issues around combinations of chemotherapy and surgery and the impact on overall survival, so would not have a direct commercial relevance for the pharmaceutical companies, but is clearly relevant from a clinical point of view.

[24] Edith Perez, MD, deputy director at large of the Mayo Clinic Cancer Center, director of Breast Cancer Translational Genomics Program at Mayo Clinic, Florida, member of Breastcancer.org Professional Advisory Board. Lead author of subsequent 2014 study on trastuzumab (Herceptin). http://www.breastcancer.org/research-news/herceptin-offers-long-lasting-benefits

Case Study 4

NeoAEGIS: MAGIC vs. CROSS: Is MAGIC or CROSS the optimum approach to AEG (Adenocarcinoma at the Esophagus and Gastric junction) and what is the added value of radiotherapy? What are the quality of life, post-operative complications and overall survival of each one?

This is a Cancer Trials Ireland-led international collaborative study (including among others Cancer Research UK), involving approximately 25 sites in Ireland, UK, France and Denmark. The study activated internationally in 2015 and has enrolled 107 patients to date of a target of 594. More partners are coming on board over time due to widespread interest in participating in this landmark trial. The study compares two treatment approaches combining chemotherapy and surgery, as follows:

The trial is ongoing and results are not yet available. Further details are at http://meetinglibrary.asco.org/content/130909-144 ; http://www.southampton.ac.uk/ctu/trialportfolio/listoftrials/neoagistrial.page ; http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-chemotherapy-before-and-after-surgery-with-chemoradiation-before-surgery-for-cancer-food-pipe-neo-aegis#undefined ; https://clinicaltrials.gov/ct2/show/NCT01726452 .

Case Study 5

ANZUP Prostate Cancer Trials, with Cancer Trials Ireland as European Sponsor

ENZAMET and ENZARAD Trials

Enzalutamide is a new hormone treatment taken as tablets. Previous trials have proven that enzalutamide improves survival and quality of life in men with prostate cancer that has stopped responding to standard hormone treatments and chemotherapy. These large, international randomized trials will determine if treatment with enzalutamide can improve survival and quality of life in men starting hormone treatment for newly diagnosed prostate cancer that, respectively, has spread and has not spread beyond the prostate. The trials are being led from Australia by ANZUP in collaboration with the Clinical Trials Centre (CTC), University of Sydney. They will involve 1,100 patients (ENZAMET) and 800 patients (ENZARAD) from Australia, New Zealand, Canada, the US, Ireland, and the UK.

https://www.anzup.org.au/content.aspx?page=trials-prostate

ENZAMET and ENZARAD

Case Study 5 (ENZAMET and ENZARAD) is another collaborative study, led by ANZUP in Australia, but with Cancer Trials Ireland as the European Sponsor. At the

time of writing there are 43 patients recruited to ENZAMET in Ireland, and 44 in the UK; expected total accruals across Ireland and UK are 275 (100 in Ireland and 175 in the UK), out of a total of 1,100. To date for ENZARAD, 15 patients have been recruited in Ireland and 1 in the UK; expected numbers across Ireland and the UK are 200 (100 in each). These patients will be the first in Europe to receive enzalutamide, which will be provided free of charge through ANZUP and the pharmaceutical company, at this stage of the disease.

Palbociclib

In the case of the Palbociclib trial (Case Study 6), disease free status at approximately 30 months was extended by a median ten months. Assuming this benefit is gained by half of the 18 Irish recruits to the trial, this equates to an additional 7.5 QALYs, and an economic value can be placed on this of €0.34 million. Follow-on trial results are expected to be published in mid-2016, so further benefits may be apparent at that point.

"So it's really this striking improvement in PFS (progression-free survival) that garnered palbociclib a breakthrough therapy designation and then expedited approval for this indication."[25]

Case Study 6

PALOMA-1 Trial: Phase 1/2, open-label, randomized study of the safety, efficacy, and pharmacokinetics of letrozole plus palbociclib (oral CDK 4/6 inhibitor) and letrozole single agent for the first-line treatment of ER positive, HER2 negative advanced breast cancer in postmenopausal women

This was an international trial of 165 women, 18 (11%) of whom were accrued in Ireland.

The findings, published in The Lancet Oncology† with Cancer Trials Ireland acknowledged as an author affiliation, were that first-line treatment with the combination of palbociclib plus letrozole extended progression-free survival by approximately 50% in patients with metastatic oestrogen receptor–positive, HER2-negative breast cancer. Palbociclib is the first approved oral CDK 4/6 inhibitor.

The results of a follow-on trial, PALOMA-2, the randomised phase III trial, will be presented at ASCO in June 2016. Combined, these 2 trials are practice-changing. Cancer Trials Ireland will also participate in the adjuvant/early breast cancer trial of palbociclib (PALLAS trial), which will enrol 4,600 women internationally through the Breast International Group (BIG).

† Finn, R., Crown, J., *et al.*, 2011, "The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study", *The Lancet Oncology,* Jan 2015 Vol. 16 No. 1 p1-116.
http://www.thelancet.com/journals/lanonc/issue/vol16no1/PIIS1470-

[25] Richard Finn, MD, Jonsson Comprehensive Cancer Center, UCLA. Lead author of above study. http://global.onclive.com/web-exclusives/finn-discusses-clinical-implications-of-palbociclib-approval-for-mbc

4. FINANCIAL BENEFITS OF CANCER TRIALS TO THE EXCHEQUER

4.1 FINANCIAL FLOWS AROUND CANCER TRIALS IN IRELAND

4.1.1 Cancer Trials Ireland Funding & Disbursements

Cancer Trials Ireland receives funding from a number of sources, namely:

- The HRB (ultimate source Department of Health),
- The Irish Cancer Society,
- Pharmaceutical companies, and
- Other funders such as the EU Commission, and philanthropic grants.

Outgoings include:

- Group Central Office (GCO) staff[26],
- GCO Overheads (non-staff costs),
- Disbursements of HRB and industry funding to hospitals.

In 2016 total funding is projected as follows:

	2016p
	€ million
Grant income (HRB, Irish Cancer Society, etc.)	3.63
Industry/Collaborative/Other Income	3.86
Total	**7.49**

For the same year its expenditure is as follows:

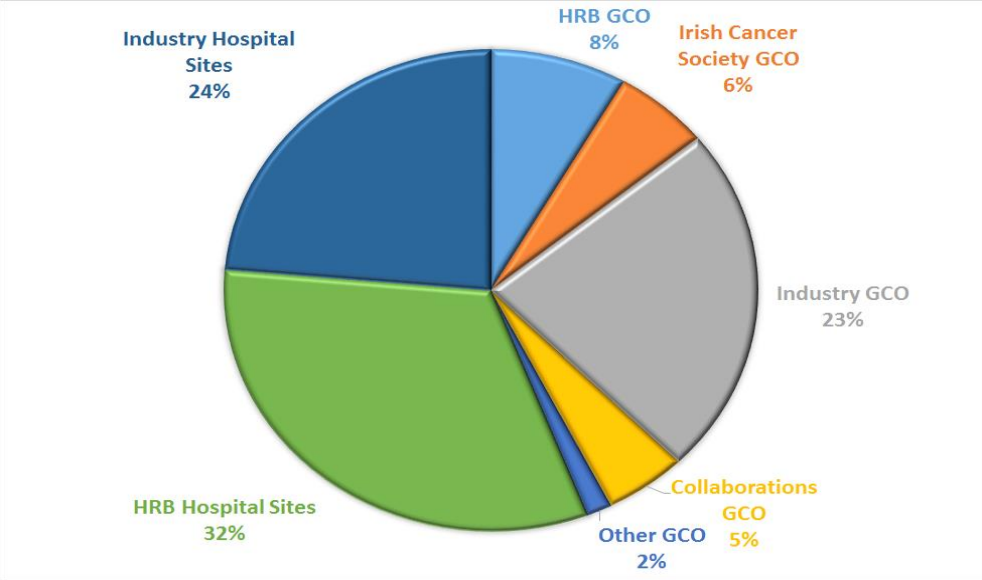
	2016p
	€ million
GCO Employee Costs	2.58
GCO Other Overheads	0.77
Hospital Disbursements (HRB & industry funding)	4.19
Total	**7.54**

p .. projected

Income from all sources, including from the HRB and industry for disbursements to hospital sites, can be presented for 2016 in Figure 4.1.

[26] Including clinical, research, statistical and data management, training, operations management, pharmacovigilance, quality control, regulation, governance, management and administration.

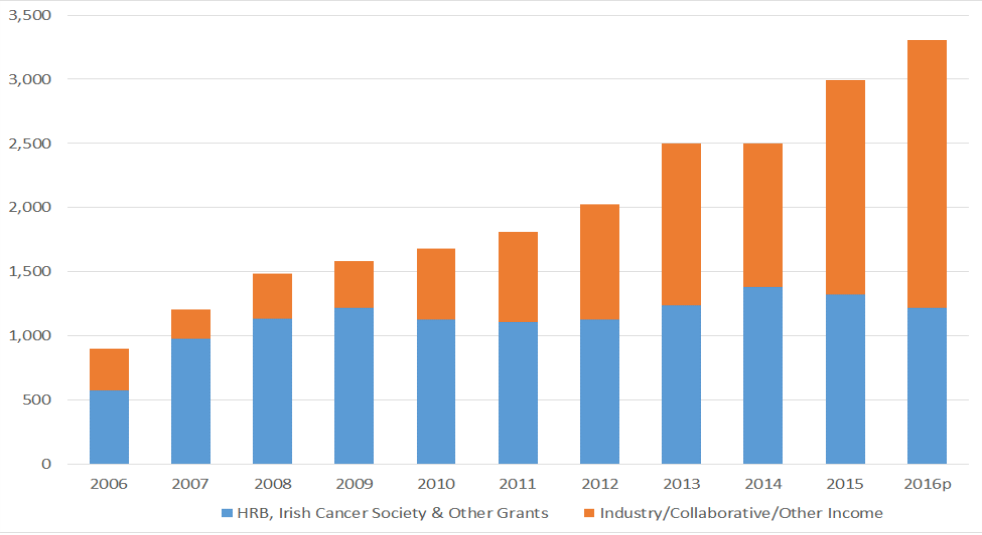
Figure 4.1: Cancer Trials Ireland Grant & Other Income (Including Hospital Disbursements) 2016p



p .. projected. Source: Cancer Trials Ireland

Cancer Trials Ireland GCO's income and expenditure match each other closely. The organisation runs a modest surplus which has averaged less than 4% of income (excluding disbursements to hospitals), over the last decade or so. The development of GCO income sources over the last decade can be seen in the graph below. It is worth noting that all of the collaborative funding is from overseas and the bulk of it is from the pharmaceutical industry.

Figure 4.2: Cancer Trials Ireland GCO Grant & Other Income (Excluding Hospital Disbursements), 2006 to 2016p



p .. projected. Source: Cancer Trials Ireland

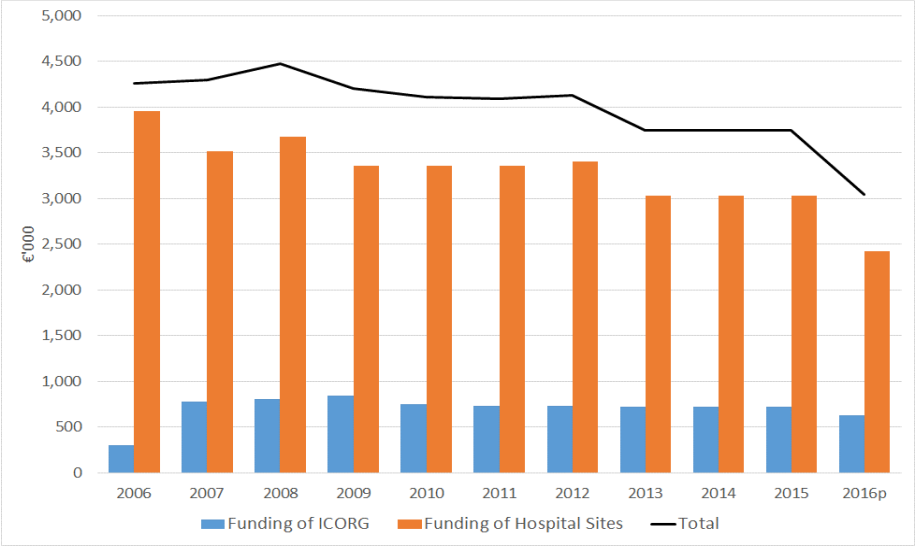
"Patients want more and better trials. They are aware that if you want advances (this will only happen) if you have patients on trials in your own country."
(patient advocacy organisation)

While Cancer Trials Ireland's activity level has grown very significantly over the period (revenues more than trebling), the bulk of this growth has been financed by

sources other than grant income. Considering only the GCO funding, in 2006 grant income represented 75% of total income, while for 2016 it is projected to represent 38% of total income.

Combining the HRB's funding of Cancer Trials Ireland Group Central Office and the hospital grants, the historic pattern of this funding source is as per Figure 4.3.

Figure 4.3: HRB Funding of Cancer Trials Ireland Central Office & Hospital Sites, 2006 – 2016p



p .. projected. Source: Cancer Trials Ireland

HRB funding has been on a downward trend over the last decade, albeit it was kept constant between 2009 and 2012, and again between 2013 and 2015. The peak year was 2008, at just under €4.5 million; by 2016, total funding will have fallen to €3.04 million, down one-third from the peak level.

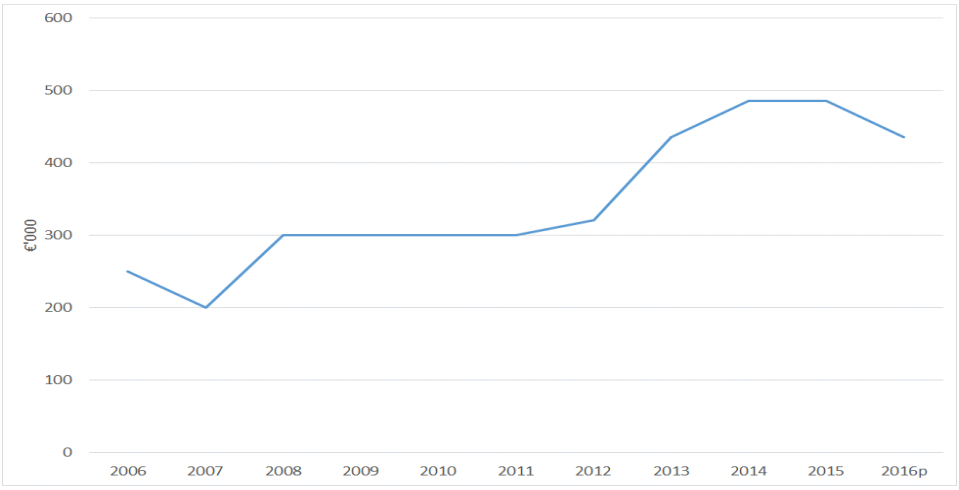
With respect to Irish Cancer Society funding, the following chart presents the historic pattern. Funding has been on a long-term upward trend, albeit it is expected to fall by 10% in 2016 (Figure 4.4).

"New immunotherapy drugs are very expensive – they're only available to patients within the context of trials". (oncology consultant, Irish hospital)

Combining this data with the historic patient accrual data from Figure 2.2, we can present the grant income funding (from the HRB and Irish Cancer Society) per accrued patient, as per Figure 4.5.

The equivalent level of grant funding per patient accrued to cancer trials in Ireland has fallen by 45% over the last decade, from a peak of €3,650 in 2009 to €2,020 in 2015. A significant further reduction can be expected in 2016, given the cut in grant income.

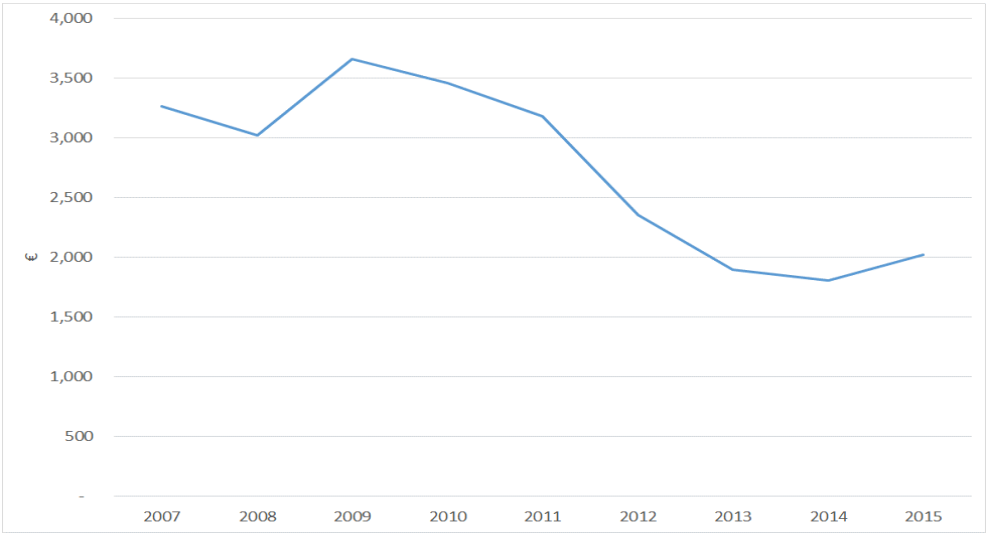
Figure 4.4: Irish Cancer Society Funding of Cancer Trials Ireland Central Office, 2006 – 2016p



p .. projected. Source: Cancer Trials Ireland

"Public patients participating in trials experience reduced waiting times for scans – this is mostly covered by the pharmaceutical companies". (oncology team, Irish hospital)

Figure 4.5: Grant Income Funding per Patient Accrued to Cancer Trials, 2007-2015



Source: Cancer Trials Ireland

Grant income from the HRB and the Irish Cancer Society plays a vital role in both Cancer Trials Ireland's and the hospital sites' functioning, as it enables them to establish the required infrastructure and meet HPRA regulatory requirements in order to be in a position to compete for international trials, as well as being in a position to undertake non-commercial and collaborative trials that do not receive pharmaceutical funding (or full pharmaceutical funding).

Noteworthy also is that €2.3 million has been awarded to Blood Cancer Network Ireland (BCNI)[27] in 2015, over a period of five years, by Science Foundation Ireland (SFI) and the Irish Cancer Society. This will support a virtual early phase trials network in sites in Galway, Dublin and Cork, with additional funding from the Irish Cancer Society for two further sites. ICORG is a partner in BCNI and will be responsible for the management and monitoring of some of the trials coordinated through the network. The first trial (CyBord-DARA) is currently in the pre-study planning phase.

Other important activities that Cancer Trials Ireland undertakes, that are dependent on the grant aid, include surveys of patient perspectives on cancer care in Ireland[28], which should help to inform patient care in Ireland going forward.

4.1.2 Pharmaceutical Industry Funding

The other main funder of cancer trials in Ireland is the pharmaceutical industry. The pharmaceutical companies fund the majority of cancer trials undertaken in Irish hospitals. The industry provides funding to both the hospital sites and to Cancer Trials Ireland with respect to trial activity. The industry funds its own sponsored trials, but it also provides most of the funding for collaborative trials. This funding generally covers:

"For the size of the industry presence in Ireland, the level of clinical trials is too low." (Irish-based FDI executive)

- Provision of drugs;
- Contributions to costs of additional tests where appropriate;
- Contributions to staff costs – payroll and training;
- Contributions to equipment and facilities investments;
- Contributions to overheads;
- Research grants and bursaries.

In addition, pharmaceutical companies:

- Will often continue to provide the drugs to trial patients after the trials are finished but before the drugs are approved for reimbursement by the Department of Health, on a "compassionate" basis[29].
- In many cases also provide free drugs and other support to investigator-led trials.

"Ireland is Tier 3 for a lot of global trials. … it is well known that oncology is better than most areas." (patient advocacy organisation)

The degree to which pharmaceutical companies pay for the costs of "standard of care", that is, the treatment that the patients in question would receive if they were not on the trial, varies. Our consultations indicate that some companies pay for this and some do not, while some will pay for elements of "standard of care".

[27] http://www.bloodcancers.ie/

[28] For example Battley, JE, *et al.*, 2015, "PO145 Cancer Trials Ireland 13-01 ABC Survey: Are We Meeting the Needs of Patients with Advanced Breast Cancer (ABC) In Ireland? A Nationwide Survey", in *Breast*; Nov2015 Supplement 2, Vol. 24, pS71-S72, 1p

[29] In some cases will also apply to non-trial patients, where a new drug that has been approved for use elsewhere is awaiting approval in Ireland, on compassionate grounds. However, this is not necessarily linked to trials having been undertaken in Ireland.

By far the largest element of pharmaceutical company funding of hospital sites is in the form of free drugs. These include drugs that are on the market and whose price is set, and novel/as yet unlicensed drugs for which a market price has not been set.

"(Hospitals in Ireland) are not viewing clinical trials as an essential part of the job". (Irish-based FDI executive)

While we have data on funding from the industry to Cancer Trials Ireland, identifying the total value of funding to the hospital sites is not straightforward, as there are commercial sensitivities around this. The Irish Pharmaceutical Healthcare Association (IPHA) indicates that industry funding per trial varies between €100,000 and €4 million, and points to five recent trials generating €10 million of income from outside Ireland[30].

One of the cancer centre hospitals has provided data which points to an approximately 3:1 ratio of industry funding to grant income (HRB etc.). In other words, for every €1 in grant funding, this hospital has succeeded in generating a further €3 in income from industry for trials. Other hospitals have pointed to a similar ratio in funding.

"Development of a knowledge-based economy, and retention of expensively trained staff require the creation of a research-driven healthcare environment". (oncology consultant, Irish hospital)

This points back to the importance of the grant aid, which provides the resources to put in place the infrastructure, and meet HPRA regulatory requirements, at which point the site is in a position to compete for commercial/international trials and related funding.

An important consideration with respect to industry funding of trials is that Ireland is competing in an international market for trials, against the range of other countries where these companies are active. As in any market, competition is on the basis of:

- price - how much the hospitals charge the firms to undertake trials (as well as the tax treatment of these costs) compared to elsewhere; and
- quality – how well the trial activity is undertaken in Ireland compared to elsewhere.

A key driver of the level of industry funding is the quality of the trial infrastructure in Ireland (centrally and on-site), and the experience of firms in undertaking cancer trials here. In this regard they report mixed experiences. Some firms have had positive experiences, one noting that it finds Ireland quicker than the UK to set up cancer trials, while another has recently upgraded Ireland to being one of its "core" countries for cancer trials.

By contrast others report less positive experiences, with under-resourcing and a lack of prioritisation of clinical research in hospitals, and as a result a reduction in the number of trials they seek to accrue for in Irish hospitals in recent years. This

[30] Cramp, R.,* 2015, "Clinical Trials - An Industry Perspective". Presentation at *HRB - building Ireland's clinical research infrastructure*, 23rd November 2015. * Scientific & Regulatory Affairs Manager, IPHA. http://www.hrb.ie/about/events/event-information/?tx_ttnews%5Btt_news%5D=649&tx_ttnews%5BbackPid%5D=567&cHash=312ff8aeb8b9fcdbb307ddb20f243cc5

may point to an unevenness in the approach and level of commitment in hospital sites across the country and possibly across specialisms.

Further analysis of the contribution of the pharmaceutical firms is contained in Section 4.2, which assesses the financial savings to the Exchequer from cancer trials.

4.2 Financial Savings to the Exchequer

A range of savings accrues to the Exchequer (in the form of the HSE) on account of clinical trial activity. Most obviously, as indicated above, pharmaceutical companies provide drugs free of charge to patients on industry-sponsored and other trials, during and in some cases after the trials. Other savings are generated in the form of contributions to salary costs, additional tests and overheads, although it could be argued that these would not have been incurred in the absence of the trials.

Savings are generated for the hospitals' pharmacies for in-patients, and for the Primary Care Reimbursement Service (PCRS) in the case of out-patients on trials[31]. There are some complications with regard to estimating the actual savings to the HSE, around such issues as:

- Where the trial drug is not generally available and a price has not been agreed with the DoH, it is not in principle easy to attach an appropriate value to it.
- Where the trial drug is not generally available, it could be argued that the benefit should be calculated by reference to cost of the "standard of care" drugs the patient would otherwise have been administered.
- In some cases patients will be administered trial drugs in addition to "standard of care" drugs, in which case it is difficult to place a value on the trial drugs (although pharmaceutical companies sometimes pay for "standard of care" drugs).
- Where drugs or other treatment approaches (e.g. TAILORx) are trialled in Ireland as part of international trials, and turn out to be successful, and their subsequent adoption generates savings for the HSE, can some of this benefit be ascribed to Ireland's contribution to the trialling process?

"Newer agents are associated with increasing costs to hospitals and the Irish health service. Hospitals that are in a position to access these drugs through clinical trials can offset some of these costs." (Oncology team, Irish hospital)

Both the individual hospitals where trials are undertaken and Cancer Trials Ireland have generated estimates of drugs and other savings to the health services over recent years. Cancer Trials Ireland estimates indicate that over the period July 2012 to December 2014 (2½ years), some €13.46 million in drugs costs savings have been generated for the Exchequer on Cancer Trials Ireland-sponsored trials. Virtually all of this was generated in the disease areas Breast (54%), Haematological (34%), and Lung cancer (12%). Annualised, this works out at €5.4 million per annum. This estimate excludes drugs provided to trial patients after the trial has ceased, but before reimbursement terms are agreed with the DoH. In some cases these can be substantial.

[31] In general, out-patients on trials would attend the hospitals for medication, whereas out-patients not on trials would normally obtain their medication from their local pharmacy.

Historically approximately 80% of trial accruals have been on Cancer Trials Ireland-sponsored trials, so on a like-for-like basis this would imply overall annual savings on all trials of €6.7 million.

"Others are trying to recreate Cancer Trials Ireland. They didn't have clinical buy-in, whereas Cancer Trials Ireland is clinically driven." (patient advocacy organisation)

Our analysis, based on data from the various hospital sites, directly and via Cancer Trials Ireland, indicates a value for drugs savings for 2015 of approximately €6.4 million. This estimate excludes drugs that are not on the market, and includes "standard of care" treatment where the pharmaceutical company has paid for this. It includes most but not all of the relevant hospitals, so it is likely to be somewhat of an under-estimate. It also excludes other payments that the pharmaceutical companies make to the hospitals for scans, contributions to staff costs, etc. It can be argued that these should not be included as they simply compensate for costs incurred by the hospitals in undertaking the trials, and therefore represent no direct saving to the Exchequer as such.

We have sought to compare these savings with international estimates of savings from participation in trials. These unfortunately are not common. One recent UK study, Liniker *et al*. (2013)[32], estimated the treatment costs savings to the NHS of 357 cancer patients recruited to 53 different interventional clinical trials at a single institution [33] (26 academic and 27 commercial sponsored; 40 phase III, 2 randomised II/III and 11 phase II design). The results can be summarised as follows:

Table 4.1: Treatment Costs Savings to the NHS per Patient on 53 Trials, 2009-2010

	Average Savings per Patient	
	Stg£	**€**
Non-Commercial Trials	-431	-493
Commercial Trials	9,294	10,629
All Trials	**4,340**	**4,963**

Source: Liniker *et al*., 2013; Central Bank of Ireland (£:€ exchange rate 2009/2010)

"There's no real career benefit for staff – they're not retained because (clinical research) is not recognised or valued." (Oncology consultant, Irish hospital)

As can be seen, the authors found that there was a modest additional cost to the NHS for patients participating in academic/non-commercial cancer trials, but a very substantial financial saving for patients participating in commercial cancer trials, amounting to over €10,000 per patient, with an overall average of just under €5,000 per patient. Costs considered in the analysis comprised mainly drugs (including dispensing and delivery), but also blood tests, scans, clinic visits and "others".

These findings relate to a significant number of commercial and academic tests, albeit at a single institution, and costs are by reference to the UK, so may differ from the equivalent costs in Ireland. However subject to these provisos, by applying these numbers to the 2,151 patients accrued to trials in Ireland in 2015, it implies a saving to the HSE of €10.7 million.

[32] Liniker, E., *et al*., 2013, "Treatment costs associated with interventional cancer clinical trials conducted at a single UK institution over 2 years (2009–2010)", in *British Journal of Cancer* (2013) 109, 2051–2057, http://www.ncbi.nlm.nih.gov/pubmed/24064969.
[33] Addenbrooke's Hospital, Cambridge.

This is well in excess of our and Cancer Trials Ireland's estimates above, and gives a fair degree of confidence that our estimates are not overstated. Hence it would appear to us to be reasonable to conclude conservatively that **savings to the HSE from cancer trial activity is approximately €6.5 million per annum.**

Further savings for the Exchequer can also be generated via more effective treatment, directly as in the case of avoided chemotherapy as a result of the TAILORx trial (see Chapter 3), and indirectly as cancer patients enjoy better health outcomes and longer lives thus reducing the financial costs to the health services of ongoing treatments.

4.3 Other Benefits for the State

The focus of this report is on quantifiable financial benefits/savings for the State of cancer trial activity in Ireland. However, other benefits also accrue, in terms of achieving health policy targets.

While it is still in the process of finalisation, we understand that the new **National Cancer Strategy** will include a target of 5% of cancer patients participating in clinical (drug) trials, with a further 5% on translational trials, over the coming years. Currently, it is estimated that in the region of 7% of patients are on translational trials; however the proportion on therapeutic clinical trials is between 2 and 3%, so there is a requirement to significantly increase numbers on trials if the national targets are to be met. In this context it is important to maintain if not increase funding.

In a similar vein, the HSE's employment of oncology consultants has increased very significantly over the last two decades, and can be expected to increase further given the expectations of growing numbers of cancer diagnoses going forward. Most oncology consultants working in Ireland at the moment have been trained overseas (mostly in the US), where clinical research is an integral part of the job[34]. In order for Ireland to remain attractive from a career progression point of view for these consultants, there needs to be scope to undertake high standard clinical research. The same is true for other health professionals working in the oncology area, such as specialist nurses and pharmacists. By facilitating this, Cancer Trials Ireland and other bodies involved in oncology research in Ireland are assisting the HSE in the recruitment of high quality staff.

[34] See for instance https://www.healthcareers.nhs.uk/explore-roles/medicine/medical-oncology

5. ECONOMIC IMPACTS OF CANCER TRIAL ACTIVITY

In this chapter we estimate the economic impacts of clinical trial activity in Ireland. The main element of our analysis relates to the economic impact of trials-related employment generated in Cancer Trials Ireland itself, the hospitals and the pharmaceutical companies[35].

We also explore other benefits qualitatively, including the attractiveness of Ireland for Foreign Direct Investment (FDI). The largest economic benefit of trials is the increased years and quality of life generated for those patients who have participated in trials in Ireland – this has been addressed in Chapter 3.

5.1 ECONOMIC IMPACTS OF TRIALS-RELATED EMPLOYMENT

Data from Cancer Trials Ireland indicates that direct employment on cancer trials in Ireland currently comprises:

Cancer Trials Ireland	49
Hospital sites	96
Pharmaceutical companies	50
Total	**195**

Thus almost 200 people are directly employed in Ireland undertaking cancer trials. We estimate that the annual payroll costs for these staff sum to approximately €10.4 million[36]. This represents the **direct economic impact**, i.e. the direct addition to Ireland's GDP on foot of this activity.

Indirect impacts arise in terms of the supply chain activity that is associated with this employment. In the case of Cancer Trials Ireland, it represents the Irish-source goods and services that Cancer Trials Ireland buys each year, plus the Irish-sourced goods and services that these suppliers buy in order to supply Cancer Trials Ireland, and so on back through the supply chain. We can use Cancer Trials Ireland's accounting information and the CSO's Input-Output Tables to estimate this. Similar

[35] Another substantial economic impact relates to the production of drugs for use in clinical trials. We have estimated that the value of drugs already on the market used in trials in Ireland is in the region of €6.5 million, but this excludes the production of non-market drugs, which would also have a significant market value. However, there are some complications with measuring an economic impact for these:

(i) since the drugs are provided free of charge, one cannot count their full market value as an economic impact (in other words the profit margin would need to be excluded), and

(ii) we do not know what proportion of these drugs are manufactured in Ireland; most of the economic impact of drugs produced outside Ireland could not be included for our purposes.

Therefore, we have excluded this impact from our analysis.

[36] Based on Cancer Trials Ireland data and CSO *Earnings & Labour Costs Quarterly, Q4 2015 (Preliminary)*, http://www.cso.ie/en/releasesandpublications/er/elcq/earningsandlabourcostsq32015finalq42015preliminaryestimates/

supply chain impacts are generated in the hospital sites and in the pharmaceutical companies, and again the Input-Output Tables enable us to estimate these[37]. Based on these the **indirect economic impact**, i.e. the addition to Ireland's GDP on foot of supply chain activity amounts to €2.6 million.

"Cancer Trials Ireland's success helps IDA build broader linkages with our existing clients and opens up opportunities for discussions with new clients interested in oncology. These deepened relationships and positive perceptions of Ireland as an innovative location have the potential to increase our chances of winning high-value FDI in the biopharma space, especially as innovation in oncology is moving at such a fast pace."
(Barry Heavey, Global Head of Life Sciences, Engineering & Industrial Tech at IDA Ireland)

Finally, the wages and salaries embodied in the direct and indirect impacts generate a further, **induced impact**, as they are spent in the wider economy. By reference again to the Input-Output Tables, we estimate that amounts to €3.6 million.

Thus the total direct, indirect and induced impacts on GDP of clinical trial activity is €16.5 million, as follows:

	€'000
Direct	10,386
Indirect	2,576
Induced	3,577
Total GDP impact	**16,539**

These indirect and induced impacts will themselves generate further employment. Based on the Input-Output Tables and the CSO's *Earnings & Labour Costs Quarterly, Q4 2015 (Preliminary)*, we estimate a further 39 Whole Time Equivalent (WTE) jobs are supported in the economy. Thus the total employment impact is just over 230:

Direct	195
Indirect & Induced	39
Total Employment impact	**234**

Finally, we can estimate the Exchequer impacts in terms of tax revenues. Based on the foregoing GDP, payroll and expenditure figures, we estimate that the related tax revenues would sum to €5.8 million:

	€ '000
Profits Taxes	697
Payroll Taxes	4,188
VAT & Other Taxes	925
Total	**5,811**

[37] The Input-Output Tables set out supply-chain impacts by NACE code sectors. NACE code 72 represents Scientific Research & Development Services, which we use for Cancer Trials Ireland and the pharmaceutical industry, and NACE Codes 86-88 cover Human health and social work services, which we use for the hospital sites.

5.2 FDI BENEFITS

Much of the funding for cancer research in Ireland, and in particular clinical trials, comes from international pharmaceutical companies based in Ireland. These companies seek to recruit patients to trials for their drugs globally, but concentrate in countries where the infrastructure to deliver high quality clinical research exists, mainly in the most developed western countries.

"On R&D, (the IPHA president) welcomes Ireland's strong structure for oncology-related clinical trials but wants to see this approach replicated in other areas." [39]

The number of therapies that have been developed to treat cancer has accelerated in recent years, and this is reflected in the improving survival rates for patients[38]. Nine of the top ten global pharmaceutical companies operate in Ireland[39], including Novartis, Pfizer, Bristol-Myers Squibb (BMS), Merck, Bayer, Roche, Amgen, Glaxo SmithKline (GSK) and Merck Serono. Many of these produce oncology drugs in Ireland or are planning to do so, reflecting the global development flow of these treatments. Indeed, a number of the manufacturing plants that were threatened by the so-called patent cliff some years ago are now active in producing these new drugs.

"The sole tool for selling Ireland (as a location for cancer trials), is Cancer Trials Ireland, as a single network."
(Executive, FDI pharmaceutical firm)

Capital investment and employment by these firms are very substantial. Multinational pharmaceutical firms employ over 24,000 people in Ireland, and IDA Ireland have indicated that several thousand of these are involved in oncology therapies.

Investments expenditure by these firms can typically cost in the €100 millions. Pfizer alone has invested over US$7 billion in Ireland since 1969[41]. Notably, BMS plans to open a new €900 million biologics manufacturing facility in Cruiserath, County Dublin, in 2019, to produce multiple therapies for the company's growing Immuno-Oncology portfolio[42]. GSK has likewise announced an investment in an existing plant in Cork that will enable the firm to produce active ingredients for newer, targeted oncology medicines[43].

Most if not all of these leading pharmaceutical companies fund cancer trial activity in Ireland. The question then arises, to what degree Ireland's cancer trial

[38] http://www.cancer.gov/about-nci/budget/plan/progress
[39] http://www.idaireland.com/docs/publications/What-makes-Ireland-Great.pdf
[40] "Pharmaceutical industry: collaborating for health", EOLAS magazine interview with IPHA President and Janssen Country Director Dr Leisha Daly, December 2014, http://www.eolasmagazine.ie/pharmaceutical-industry-collaborating-for-health/
[41] http://www.idaireland.com/docs/publications/What-makes-Ireland-Great.pdf
[42] http://www.biopharmachemireland.ie/IBEC/Press/PressPublicationsdoclib3.nsf/wvPCINewsByTitle/bms-and-nibrt-launch-E1-million-collaboration-01-04-2016?OpenDocument
[43] http://ie.gsk.com/ie/media/press-releases/2016/gsk-unveils-two-new-state-of-the-art-facilities-following-12m-investment-at-its-cork-site/

infrastructure has helped in attracting multinational pharmaceutical firms to operate (or continue operating) in Ireland.

"A high percentage of the world's 'blockbuster' medications are produced (in Ireland) and the industry has seen a successful transition from traditional small molecule drug manufacturing to development and manufacture of biotech drugs and high potency 'nichebuster' products."[44]

Our discussions with industry and with IDA Ireland, indicates that while the scope to recruit to clinical trials in Ireland is a help, in general it is not a decisive driver in attracting multinationals to locate facilities in Ireland. IDA Ireland officials could however identify one case where participation in clinical trials was a significant factor in a firm's decision to locate activities in Ireland, with significant employment consequences.

Looking forward, IDA Ireland does see the likes of Cancer Trials Ireland as being more influential in attracting FDI to Ireland. They are actively targeting:

(i) Global shares for major firms including pharmaceuticals. Relevant activities for the latter include medical writing and regulatory compliance.

(ii) Specialist international services companies, including Contract Research Organisations (CROs), which manage clinical trials internationally. Firms in this sector already active in Ireland are ICON, employing 800 people in Ireland (http://www.iconplc.com/), and Quintiles, employing 200 (http://www.quintiles.com/locations/ireland).

The IDA sees having organisations such as Cancer Trials Ireland and staff trained in clinical trials in Irish hospitals, as being important in attracting these activities to Ireland.

"Ireland is not really on the radar (for clinical trials), except in oncology".
"We need Cancer Trials Irelands in other areas, but not at the expense of Cancer Trials Ireland".
(Barry Heavey, Global Head of Life Sciences, Engineering & Industrial Tech at IDA Ireland)

Other Economic Benefits of Trial Activity

5.3.1 International Grants

Cancer Trials Ireland is a key element/driver in a number of grant schemes from the likes of Irish Cancer Society (BreastPredict, iProspect) and SFI (Molecular Therapeutics for Cancer Ireland [MTCI] 2009 – 2014). Since these are grants awarded from within Ireland, they do not of themselves generate economic benefits for the Irish economy. However, Cancer Trials Ireland has also been successful in winning overseas funding, and this does generate a direct benefit for the Irish economy.

ANGIOPREDICT[45] is an EU Commission 7th Framework Programme[46] (FP7) project which ran from March 2012 to February 2016. It involves a number of Irish[47] and international partners. Cancer Trials Ireland played an essential role in winning this funding, since it managed a retrospective sample collection from Germany, The Netherlands and Ireland, and ran a translational trial in Germany and Ireland. This trial is now in follow-up and is due to end in February 2017. Cancer Trials Ireland earned €320,000 in funding under ANGIOPREDICT, while all the Irish partners

[44] http://www.idaireland.com/docs/publications/What-makes-Ireland-Great.pdf
[45] https://www.angiopredict.com/
[46] https://ec.europa.eu/research/fp7/index_en.cfm
[47] Irish partners in addition to Cancer Trials Ireland are RCSI, Oncomark Ltd. (http://www.oncomark.com/), the Conway Institute of Biomolecular and Biomedical Research, UCD and Pintail Ltd. (http://www.pintail.eu/cms3/).

together earned €3.43 million, out of a total fund of €6 million. These earnings can be seen as a direct benefit to Ireland's economy. The funding earned by the other Irish partners is likewise a benefit to the Irish economy.

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