CLINICAL RESEARCH INFRASTRUCTURE IN IRELAND
REMAINING BARRIERS, POTENTIAL SOLUTIONS
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1. The report and its aim

On 13 May 2008, more than 200 delegates from patients’ organisations, industry, science and public policy met in Dublin Castle to discuss how Ireland is to become globally competitive in clinical research. The meeting was organised by the Irish Platform for Patients’ Organisations, Science and Industry (IPPOSI) in association with the Irish Pharmaceutical Healthcare Association (IPHA).

The task the meeting set itself was, in the words of IPPOSI Chair Michael Griffith, to take stock of: “What are the major deficits still to be faced and how are we going to tackle them?”

Delegates were addressed by Minister for Health and Children, Mary Harney, TD, who stressed the value of collaboration: “In a country as small as this I’m interested in people working together.” Everybody has a common goal, she said – to improve healthcare and improve access to new medicines, and that, she said, makes research “very much a front-line activity”.

IPPOSI is not a lobbying organisation: it is a platform for discussion between patients’ organisations, scientists and industry and, wherever possible, with State agencies. The idea is to achieve consensus through discussion of matters of mutual interest. This report is, accordingly, a report of the discussion that took place and, crucially, the policy recommendations that emerged.
2. Executive summary

The starting point for any discussion about clinical research is the needs of patients. Introducing the conference, IPPOSI Chair (former CEO of Fighting Blindness) Michael Griffith stressed that Irish patients want a world-class clinical research infrastructure in Ireland – and he reminded the audience that we are all, or at some time will be, patients.

Yet in Ireland the lack of that infrastructure contrasts sharply with Ireland’s position as one of the world's most attractive locations for pharmaceutical manufacturing. Worse, as Anne Nolan, CEO of IPHA, said, Ireland is losing its attractiveness for clinical research. The result, she said, is that “Irish subsidiaries find it increasingly difficult to compete internally, to convince corporate headquarters to conduct clinical research in Ireland.”

The good news is that all the building blocks of a good infrastructure seem to be in place, with huge investment in recent years. Building blocks are not enough however: Ireland also needs to provide strong leadership for a clear national strategy that can remove the barriers and take advantage of the real opportunities that exist.

Consensus on where the problems lie and what the solutions might be, was not hard to find. On the contrary, the remarkable thing about the day’s discussion was the extent of agreement. Equally remarkable - the proposed solutions are not only straightforward, they are not inherently expensive.

Five clear individual recommendations emerged from the discussions …

1. Standardise Ireland’s system of Ethical Review Committees and remove their unpredictability.

2. Create formal career structures for health professionals interested in research, especially (but not only) for research nurses.

3. Integrate internationally accredited training in Good Clinical Practice into medical and nursing education at all levels.

4. Introduce practical and standard indemnity arrangements for clinical trials, in particular for non-commercial clinical research.

5. Make research a core value in healthcare.

…and one overarching recommendation

6. Appoint a clinical research “supremo” in the Department of Health and Children – along the lines of the UK’s Director of NHS R&D – with the power to remove the roadblocks and create and deliver a research strategy for health in Ireland.
3. Foreword: The patient view

The scene was set with a video of Jennifer Moran, a young woman with multiple sclerosis (MS) who spoke simply and movingly about her disease and her experience with clinical research. She described how she had become aware of her disease. She noticed that she had begun to limp and that her feet were cold. She could feel her hand–eye coordination deteriorating along with her confidence. She had no idea what was going on or why this was happening.

Jennifer took part in a clinical trial, one drug versus another, and her mood changed. “I felt I was wrapped up in cotton wool,” she said adding that for the two years of the trial there was “never a problem” and that she was well looked after. Her account made clear how important the role of the research is to patients.

Her family had been against her taking part in the trial. “Don’t be a lab rat,” they said.” Then she started explaining to them what the trial was about and their attitude changed.

Would she take part in another trial? “Definitely,” she said. Now on a new drug, she did not have words to describe how relieved she now feels. “I can go and do what I want to do. Last year my MS was dismal. Now I feel that I can walk, I can talk, I can study, I’m back to being me again.”

4. Update on Ireland’s clinical research infrastructure

The good news is that Ireland has come a long way in recent years, as Professor Bill Powderly, Head of the School of Medicine and Medical Science at University College Dublin, explained: “The building blocks have been developed.”

Professor Tim O’Brien from University College Galway agreed, referring to “huge investment”. But you need more than building blocks. “Clinical research”, said Powderly, “is collaborative”: without the structures to involve patients, physicians, nurses, and others, it won’t work.

“There are important economic goals that would accrue from a vibrant clinical research structure,” he said, adding a warning note: “It’s not as if the competition has stood still in the last five years… Ireland has gone from being potentially ahead to considerably behind in this global marketplace.”

Another key requirement is to generate critical mass, as, for example, with Molecular Medicine Ireland, a partnership between NUI Galway, the Royal College of Surgeons in Ireland, Trinity College Dublin, University College Cork and University College Dublin... with the mission of speeding up the transfer of knowledge from the bench to the bedside. People are critical to
this mission. “How do we train our people?” asked Professor Noel Caplice from University College Cork. “How do we get clinical researchers speaking the language of patients?”

The key, according to Professor Dermot Kelleher, Professor of Clinical Medicine at Trinity College Dublin, is to reward excellence in research, to build what he called “the human capacity for the next generation of biomedical researchers” by integrating a culture of research into biomedical education and training. “The physical capacity is further advanced than the human resource capacity,” he said.

But this is where the roadblocks appear. Ireland is not only short of research nurses – a defect that training can remedy – but the Health Service Executive’s new staff ceilings make it difficult to get approval to hire them. That’s not the only area causing concern. “We have had two years where we haven’t been able to move on clinician investigator posts,” said O’Brien.

The solution for Ireland’s economy as well for its healthcare, is to sort out the country’s priorities, said O’Brien, taking cognisance of the existing strengths and then putting in place single governance structures and streamlining funding for health research. Partnership is essential, including with Northern Ireland.

From industry, a warning: Dr. John Farrell, Medical Director of Pfizer, said we need to be clear about what we can deliver and what we cannot. “We need to be able to persuade Pfizer New York that Ireland is a good place to invest money in...If Pfizer does trials in the UK and they fail, they will still do more. If we fail in Ireland it will be much more difficult next time around,” he said.

That means looking at infrastructure – especially people, “and especially research nurses”. It is still, said Farrell, “extremely difficult” to get good people to work in research and industry. But it has to be done: “Clinical research shouldn’t be seen as something nice to have but, as something that Ireland should be involved in.”

From the North, Dr. Michael Neely, Operational Director of Health and Social Care R&D, repeated the message about delivering on promises. He also described how they took a fresh look at Research Ethics Committees, starting with a clean sheet of paper. The result: they stood down the existing committees and created just three for Northern Ireland, supported by a common office. “That has really simplified the process,” said Neely and provided a single set of governance issues.

In the Republic of Ireland there are around 57 different Ethics Committees. The ensuing diversity constitutes one of the big barriers to Irish clinical research, but thus far, said O’Brien, “I don’t sense a lot of progress.”

On this, and on other issues, the overarching problem is the lack of a driver. Professor Dermot Kelleher summed up the feeling. “You only have to look at the change in the UK since Sally Davies took over health R&D”, he said: one person “with the energy and drive to have a transformational effect...There is a research strategy explicitly and implicitly in the NHS now, focused on strengths. We need someone in that kind of position in the Department of Health and Children to drive that forward.”

Professor Muiris Fitzgerald, the former Chairman of the committee set up by the Health Service Executive to recommend what role research should play within the new organisation, said one key proposal in the committee’s report is “a research unit within the HSE at the centre of the organisation with a high level leader along the lines of the Sally Davies model”, adding, “I do think that this particular coalition here today of patients, science and industry should use all the leverage possible to give support to the development of that unit.”
5. Conducting clinical research in Ireland

From industry again, another warning: despite wonderful research centres, said session chair, Dr. Tracy Cunningham, Medical Director of GlaxoSmithKline, a number of companies have downgraded or stopped undertaking clinical research in Ireland. “Now is a good time for Ireland Inc. to take a good look at this process,” she said. The challenge for companies is to do high quality studies that benefit patients while meeting regulatory requirements. Tolerance of underperformance is lower than ever and Ireland has to be “on top of its game”.

Dr. Peter Doran, Scientific Director of University College Dublin’s Clinical Research Centre laid down a challenge for the audience: “For us to be successful, and for our patients to have better outcomes, the people in this room today are the people who will make it happen,” he said, applauding IPPOSI’s vision in organising the meeting.

Based on his experience in Dublin, Doran said the key to success was communication with all stakeholders. “Spend time building relationships”, he said, adding that UCD also has superb infrastructure and very strong “human capital”. What’s needed to capitalise on the opportunities for Ireland? “Full engagement”, he said, “core multi-annual recurrent funding, ethical standardisation and expertise and resources for completion of submissions to regulatory bodies and, more clinical investigators”.

In an overview of the challenges and constraints facing clinical research in Ireland, Professor Dermot Kenny, Director of the Clinical Research Centre of the Royal College of Surgeons in Ireland reminded the conference that in the late 1800s Dublin had been a leading centre for clinical research. He stressed that clinical research is driven by clinical questions, rather than abstract science. Focus on the clinical problem, he suggested, giving examples from heart disease and lung cancer. Kenny, too, paid tribute to the crucial role played by research nurses.

For Dr. John Stinson, Medical Director of LEO Pharma, Ireland had many strengths, with big changes in the past 12 years. He pointed to high standards among clinicians and scientists, altruistic patients and population, a desire to think creatively and, from pharma, a great hunger for trials and funding.

But, he said, there were many weaknesses, underlining previous contributions: on indemnity, Ethics Committees, different requirements for submissions, the freeze on recruiting clinical staff (“Are [the authorities] really interested in research or trying to put out the fires?”); and in relation to the lack of career structures and training, especially in Good Clinical Practice. “We all say the right things,” said Stinson, “but do we really walk the walk?”

“There are opportunities”, said Stinson, “with more consultants and much better hospitals than 20 years ago, more funding for science and an entrepreneurial population”. The challenge is to move up the value chain, more towards Phase II rather than Phase III trials.

There are threats: new countries joining the EU, Ireland’s small population, the lack of protected time for research and the shortage of clinical research positions. For patients, that could add up to fewer opportunities to take part in clinical trials and less access to the newest medicines, especially for rarer diseases.
If anyone still needed convincing about the relationship between infrastructure and output, Dr. Brian Moulton, CEO of the All Ireland Cooperative Oncology Research Group (ICORG), provided the evidence with two simple slides: the first showed how investment – first from charities, then from the Health Research Board – had led to an increase in clinical research staff; the second slide had an almost identical curve showing an increase in the number of patients enrolled. The barriers though had not disappeared: the “hospital focus” that regards research as a luxury, the lack of critical mass, problems with staff retention and the lack of protected time for research. He also singled out as barriers, the lack of a single ethical opinion for certain kinds of clinical research and the Health Service Executive’s block on new posts, even if not funded by them.

One thing was made crystal clear: patients want to see clinical trials. “We know that clinical trials are vital to therapeutic advances,” said Christine Murphy-Whyte, Chairperson of Europa Donna Ireland, the Irish Breast Cancer Campaign. For her, transparency was an important issue. Patients, she said, want up-to-date and clear information on trials that are relevant to them – but often they neither know about trials, nor are they asked to take part in them.

Ireland certainly needs to get better at recruiting patients for clinical trials, said John Kiernan, CEO of Quintiles. The company employs 1,000 people in Dublin to design and manage clinical trials – but carries out the trials abroad. He called for better education about trials, both for patients and for healthcare professionals.

A key clinical problem is the lack of research nurses. Dr. Marion Rowland from Our Lady’s Children’s Hospital, Crumlin, drew applause from delegates when she said that Ireland will remain in the clinical “Dark Ages” unless there are nurse researchers collecting data, having career structures and working as real partners.

“Absolutely” agreed Doran: “We have been complacent about this.” But he pleaded for recognition of the backdrop: “For us to create a career structure for a research nurse when we are living on two-to-three year funding is pretty difficult.”

Once again, the topic of leadership arose. “We need some long-term political thinking,” said Stinson. “A Tsar in charge of research.” The days of computer and pharma manufacturing are going he said and, Ireland needs to move up the value chain.
6. Making Europe competitive in clinical research

Ireland may be an island geographically but, in research terms, its fate is strongly connected to Europe. “Europe is important for Ireland and, Ireland is important for Europe,” underlined Dr. Ruth Barrington, Chief Executive, Molecular Medicine Ireland, introducing the discussion on European competitiveness. Echoing Mary Harney’s earlier comments about collaboration, she said, “Some people think research infrastructure is a large instrument. For us it is networks, linking the high quality sites and equipment to make something much more significant.”

For Professor Jacques Demotes-Mainard, Director of the European Clinical Research Infrastructures Network (ECRIN), infrastructure is one of the three challenges the European Union faces in clinical research, singling out the legislative framework and funding as the other two key issues.

The legislative framework is set by the 2001 Clinical Trials Directive. Aspects of the Directive work well, said Demotes-Mainard – but his list of what doesn’t work was much longer, headed by the lack of harmonisation and the fact that as a Directive it is subject to interpretation when carried over into national laws. He called for a Regulation, which would have the same effect in all countries of the EU. He was concerned too, that since medicines are classified as “products”, the Directive is under the aegis of DG Enterprise of the European Commission. With other legislation prepared by health ministries, he said, “We need legislation that protects patients in the same way.”

Demotes-Mainard is also one of the leaders of the ICREL project, funded under the European Union’s Framework Programme 7 (FP7), which is looking into the impact of European legislation on clinical research. The results of its survey will be ready for discussion in December 2008.

ECRIN has its Irish counterpart, ICRIN, and its coordinator, Margaret Cooney, was on hand to explain its work and to put forward a number of recommendations. Like others, she wanted reform of the Research Ethics Committee infrastructure – “Obviously there is a problem,” she said, calling the current system a “significant roadblock”. She wanted a central supervisory body, set up by the Department of Health and Children, which would triage proposals for all categories of clinical research and then pass them on to “a reduced number” of Ethics Committees for a single opinion.

Cooney called for the creation of a resource for nationally accredited training in Good Clinical Practice for research staff in hospitals and primary care. It would not be expensive, she said: one full-time equivalent trainer financed to go round the hospitals in line with the rotation of registrars “would make a huge difference commercially and academically”. She also wanted a nationally accredited standard for medical laboratories and, an umbrella organisation to facilitate all disease control and biobanks under a standard governance structure, with a transparent access policy to translate discoveries.

The need for training was underlined when Dr. Elaine Breslin, Medical Assessment Manager at the Irish Medicines Board, talked about the reasons its inspectors found for poor compliance with the regulations: lack of resources, poor monitoring and poor understanding of the legislation and guidance. She also echoed the concerns expressed by Demotes-Mainard, supporting the harmonised approach to the assessment of clinical trials.

When it comes to medical devices the responsibility for ensuring that they meet the requirements of the Directives rests with the National Standards Authority of Ireland (NSAI) which is the Notified Body for Medical Devices in Ireland. Its Medical Director, Dr. John O’Dwyer highlighted a paradox: with small trial sizes (generally around 100 people) and a large devices industry (employing 26,000, 11 per cent of the country’s manual workforce) Ireland should be ideal for clinical trials of medical devices. Instead, companies prefer to go to countries like Germany, Belgium and Poland that, he said, have “dealt with the
barriers that need to be overcome to make the place attractive”. Ireland, meanwhile is seen as complex, he said, adding, “It shouldn’t be. It should be attractive.”

A study by the Medical Devices Clinical Trial Taskforce involving the NSAI and the Irish Medical Devices Agency in 2006 highlighted nine barriers, headed by poor infrastructure and incentives for Principal Investigators, poor public perception of the benefits of clinical research, lack of expertise in Ethics Committees and a shortage of experienced research nurses, who lacked a proper career path. He also pointed to delays occasioned by sequential review – first by the Ethics Committee, and only after by the Competent Authority – while competitors had changed their laws to allow parallel review and, with it, faster processing.

Dr. O’Dwyer called for the establishment of one facility as a central point of contact for companies considering clinical trials, as is the case in several EU countries, and one point of contact also for hospitals on issues such as ethics, indemnity, IP strategy, and commercialisation. In addition, he wanted more funding for R&D via tax credits for the health service.

“We have everything we should have,” said Dr. O’Dwyer. “We need networking and synergy between stakeholders to overcome the barriers and provide key solutions.”

Mention of resources was the cue for Professor Kurt Zatloukal from the Medical University of Graz, Austria, to talk about Europe’s new Biobanking and Biomolecular Resources Research Infrastructure (BBMRI). Its mission: sustainably secure access to biological resources for health-related research to improve the health of Europe’s citizens.

With a small headquarters staff, the BBMRI relies on networking – what Zatloukal called the “hub-and-spoke approach”, with individual biobanks connected with other biobanks, such as cancer biobanks, that have common interests. There might also be associated partners such as hospitals, universities and service providers. Biological samples are central to medical research – but it might take changes to national legislation to ensure that tissue and other samples are collected in routine medical service.

7. Afterword: The problem of Ethics Committees

In the short time left for discussion at the end of the day, the focus was on Ireland’s Ethics Committee system, identified by many as an important roadblock to progress.

The trouble is, there is no guidance yet at the European level on a system of accreditation for the committees. Professor Jacques Demotes-Mainard said they differed from country to country, with some responsible for the process of informed consent and also for assessing the research methodology. The variation is not only between countries, said Margaret Cooney – the roles of the committees also differ within Ireland. Harmonisation, said Demotes-Mainard, would be a step towards implementing better quality through training.

The frustration is shared by members of the Research Ethics Committees themselves, summed up from the floor of the meeting by Gillian Vale, administrator for the Ethics Committee at Beaumont Hospital. Vale said that the committees agreed with many of the recommendations being made – “We’re just waiting for someone with the power to get them implemented.” And that, she said, “never seems to get done”. Twelve of Ireland’s 13 Research Ethics Committees recognised by the Department of Health and Children under the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 have adopted a common application form, even though, she said, “no one at the Department pushed it”. The Irish Council for Bioethics has designed a programme for all Research Ethics Committees to develop training, she said, but cannot get anyone to fund it.

The message: one that ran through many presentations during the day – that Ireland needs a single person, as in the UK, in a responsible, national position and with the clout to implement the recommendations so clearly and consistently being advanced by the clinical research community.

Peter Wrobel, Rapporteur
Some feedback from delegates...

**Patients’ Organisations**

“Well done to all on an excellent conference.”
- Ms Christine Murphy-Whyte, Chairperson, Europa Donna Ireland.

“The content was excellent...”
- Mr Godfrey J. Fletcher, CEO, The Cystic Fibrosis Association of Ireland.

**Other**

“Warmest congratulations on the success of yesterday’s conference. It was a most stimulating and energising meeting, and demonstrated to me the hunger that is out there to overcome the barriers to a thriving clinical research environment in Ireland.

Bringing all the parties together in the way that you did was a brilliant idea. The suggestion here today is that it should become an annual event! It could become the annual check-up of clinical research in Ireland. It was also a pleasure to work with you!”
- Dr Ruth Barrington, Chief Executive, Molecular Medicine Ireland.

**Science / Academic**

“You can add my appreciations to the list too!!! I have told a number of people that it was one of the best one-day meetings I have been at for a long time! Congratulations.”
- Prof Leslie Daly FFPH, Professor of Epidemiology and Biomedical Statistics, UCD School of Public Health and Population Science, UCD.

“Many thanks for the invitation. I would second the comments that this is one of the most important meetings on this subject held in Ireland. It was really important to have all the different constituencies in one room. Congratulations on the organisation which was excellent.”
- Prof Dermot Kelleher, Professor of Clinical Medicine, Trinity College Dublin.

**Industry**

“Thank you again for the excellent meeting... It was one of the most valuable days I have spent and hopefully it will lead to further developments.”
- Dr Greg Hays, Medical Director, Astellas Pharma.

“Thank you for the opportunity to attend the excellent IPPOSI day last Tuesday. It was very interesting, educational and dynamic. Congratulations to the IPPOSI team on an educational, thought provoking and high quality conference.”
- Mr Ronan Donelan, Director, Global Operations, Global Regulatory Affairs, Quintiles Global CRO.
RECOMMENDATIONS:

1. Standardise Ireland’s system of Ethical Review Committees and remove their unpredictability.

2. Create formal career structures for health professionals interested in research, especially (but not only) for research nurses.

3. Integrate internationally accredited training in Good Clinical Practice into medical and nursing education at all levels.

4. Introduce practical and standard indemnity arrangements for clinical trials, in particular for non-commercial clinical research.

5. Make research a core value in healthcare.

...and one overarching recommendation

6. Appoint a clinical research “supremo” in the Department of Health and Children – along the lines of the UK’s Director of NHS R&D – with the power to remove the roadblocks and create and deliver a research strategy for health in Ireland.