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RCTs 'on an undeserved pedestal'

'Judgement needed' in analysis of evidence

Professor Sir Michael Rawlins, Chair of the UK's National Institute for Health and Clinical Excellence (NICE) has called for both investigators and decision-makers 'to accept that the interpretation of evidence requires judgement.'

Giving the annual Harveian Oration at the Royal College of Physicians (London, UK, 16 October, 2008), he pointed out the limitations of randomised controlled trials, and rejected the trend to use hierarchies of evidence in the development of clinical guidelines. 'Hierarchies attempt to replace judgement with an over-simplistic, pseudo-quantitative, assessment of the quality of the available evidence,' he said (*Harveian Oration, 2008, ISBN: 978-1-86016-347-0*). They 'place RCTs on an undeserved pedestal.'

'THERE HAS BEEN REMARKABLY LITTLE RESEARCH ON HOW WELL RCTS PREDICT BENEFITS IN EVERYDAY USE'

Speaking to *EJC* after the Oration, he stressed the importance of RCTs. 'I'm not for a moment saying they're wrong or unnecessary. But they do have limitations and everyone needs to be well aware of what they are.'

The main problem is generalisability, he said: the extent to which results from a RCT are applicable in a wider context. Women, older people and ethnic minorities tend to be under-represented in RCTs, and those with co-morbidities are often excluded. 'There has been remarkably little research on how well RCTs predict benefits in everyday use.'

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Further: 'We know in fact that RCTs are not good at picking up adverse effects of drugs, they are remarkably poor at this, especially for less common effects and those with long latency,' he said.

Other issues include the substantial cost of RCTs in time, money and energy, and the fact that it may be impossible to carry out RCTs for treatments of very rare diseases. They may be unnecessary when a treatment produces a dramatic benefit, such as imatinib (Glivec) for chronic myeloid leukaemia.

A particular problem in oncology is the number of trials which are stopped early, either because a drug isn't working or because of side effects. 'Only one in three trials of cancer drugs goes to its planned termination. I'm not saying they shouldn't be stopped – there are good reasons why trials are stopped – but the big difficulty is that there is no consensus among statisticians on the circumstances under which trials are stopped early. We do not have widely accepted rules or statistical tests for determining this.'

'HIERARCHIES GIVE AN OVER-SIMPLISTIC, PSEUDO-QUANTITATIVE, ASSESSMENT OF THE QUALITY OF EVIDENCE'

There are 'serious pitfalls' in deciding to terminate a trial early, he said. If an interim analysis shows an unexpected benefit, it may be difficult to distinguish a true effect from chance – a random high. Stopping trials early for benefit may systematically overestimate treatment effects and there is 'a real danger' that claims for benefit may be inadvertently unwarranted, he said.

Prof Sir Michael Rawlins

'In cancer, this is particularly important as we are often talking about relatively modest benefits. One does need to be very certain that in routine practice, the promised benefits can be delivered.'

RCTs have had a profound influence on the practice of modern medicine, but Sir Michael said that the prominence awarded to them in hierarchies of evidence is 'unreasonable'. He quoted Bradford Hill, the architect of the RCT, who said, 'Any belief that the controlled trial is the only way would mean not that the pendulum had

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Workload reduced by updated RECIST

The updated criteria for assessing tumour size in clinical trials, RECIST 1.1 (Response Evaluation Criteria in Solid Tumours) reduces the number of measurements required per patient from 10 to 5. The authors stress that while this has major implications on workload, it will have no impact on study outcomes.

The updated RECIST are due to be published in an *EJC Special Issue* (2009;**45**:2) and outline a number of key amendments:

- Number of target lesions for assessment of response reduced from 10 to 5. Exceptions are discussed;
- New guidance on how to make robust measurements of lymph nodes;
- More explicit guidance on how to evaluate the tumour burden in randomised trials in which disease may not be measurable and progression of disease is the primary endpoint;
- In randomised trials, the obligation to confirm response at 4 weeks is removed;
- The definition of progression has been refined so that it not only includes a 20% increase in size of lesion, but also 5mm absolute increase (apparent changes of a few mms may be within the range of measurement error);
- More details on imaging and the implementation of the guidelines.

Dr. Elizabeth Eisenhauer

Guest editor, Dr. Elizabeth Eisenhauer (National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada), stressed that the recommendations are evidence-based: 'They are grounded in the evidence base and where it didn't exist – as was the case in some areas – we set about to create it. The EORTC Data Center undertook to create a warehouse of data from clinical trials of solid tumours from both industry and cooperative groups. We were able to test the recommendations on these data to look at the impact of proposed changes and decide whether the evidence supported the change or not.'

The reduction in the number of lesions to be measured, for example: 'This will have a big implication for the workload in clinical trials and we found that it will have no impact on described study outcomes. This change can be made without loss of information,' she said.

The RECIST *Special Issue* covers CT, MRI and PET scanning, but in the context of anatomical, rather than functional imaging. Dr. Eisenhauer: 'The imaging experts on the RECIST working group advised that the state of evidence does not support a move to replace anatomical with functional imaging criteria as yet. For the foreseeable future, tumour assessment in trials will continue to be largely determined by changes in size. The most compelling data set at present supports anatomical imaging.

'Functional imaging needs further validation to determine whether it could substitute anatomical measurements, or complement them in ways that would make the overall assessment more predictive of what happens in terms of patient survival.'

A discussion paper within the *Special Issue* describes the process and the level of evidence that will be needed before functional imaging can supplant anatomical imaging in clinical trials.

The whole point of RECIST is to improve the consistency and standardisation of trials, Dr. Eisenhauer said: 'Drug development and clinical cancer research is a global enterprise. The more consistent we are in describing what we have seen, and in using the same measures and endpoints, the more reliably we are able to interpret the results from a variety of sources.'

RCTs 'on a pedestal' *(Continued from page 1)*

swung too far but that it had come right off the hook.'

There are other ways to establish the effects of an intervention. Observational studies, including historical controlled trials and case controlled studies, can provide an important source of evidence about both the benefits and harms of interventions, he said. Care is needed in the interpretation of results, though: 'For the future we need to develop approaches that allow us to be confident that the results of observational studies generally, and case-control studies in particular, can provide information that permits reasonable assumptions about internal validity.'

Sir Michael ended his Oration with a call for hierarchies of evidence to be replaced by a diversity of approaches. This was not a plea to abandon RCTs: 'Rather it is a plea to investigators to continue to develop and improve their methodologies; to decision makers to avoid adopting entrenched positions about the nature of evidence; and for both to accept that the interpretation of evidence requires judgement.'

Helen Saul

EUROFILE

Research councils tackle clinical trials directive

Europe's medical research councils are putting together a set of recommendations to address the problems of conducting international non-commercial clinical trials. Due at the end of 2008, their report will be sent to the European Commission and national governments, and will include measures to tackle the financial and administrative burdens placed on health professionals by the European clinical trials directive.

The clinical trials directive came into force in 2004. It required one person or institution, a sponsor, to assume the legal and financial responsibility for running a trial across all study sites. This increased the burden on non-commercial clinical trials as institutions had previously shared these costs. In addition, the fragmented implementation of the directive by member states has made multi-national collaborations more difficult, increased paperwork and delayed the start of trials.

The European Medical Research Council launched its initiative in 2007 to collate best practices and provide a Europe-wide approach to assessing the problems. It resulted in five strategic workshops in April 2008. The remedial measures stemming from the workshops were discussed at a closed consultation with stakeholders supported by the French presidency of the European Union, at the end of September 2008 in Strasbourg. They were due to be translated into concrete actions by a steering group meeting in Frankfurt, November, 2008.

'A MULTIPLE-SPONSOR SYSTEM COULD ALLOW ONE ORGANISATION PER COUNTRY TO TAKE RESPONSIBILITY'

The EMRC made two recommendations on refining the sponsorship of non-commercial clinical trials. The first proposes a legislative change to allow for a European body such as the European Medicines Agency, EMEA, to act as a sponsor for non-commercial trials.

The second proposes a multiple-sponsor system with one organisation per country taking the responsibility for participants from that country, in the trial. The trial would also have a designated lead sponsor to oversee and co-ordinate management. Several member states' interpretation of the legislation already allows for this. According to Stefan Bielack, project leader of the European Science Foundation's study on osteosarcoma, this lead role would be suited to large research institutes or teaching hospitals as they already possess the requisite infrastructure. The system could be implemented at national level, based on agreement between member states.

EMEA is supportive of the EMRCs work. Fergus Sweeney, principle scientific administrator at the EMEA inspections sector says 'We're keen to find ways of supporting the EMRC, help solve problems and streamline procedures.' However, taking on the role of sponsor for non-commercial clinical trials 'is a research institute type role,' he says. 'EMEA would require a new legal mandate.'

The directive introduced stringent reporting of adverse drug reactions: changing this is high on the EMRC list. Reporting obligations still stop short of what is needed to judge the efficacy of the drug in complex conditions. 'This is a big, big issue for the cancer community,' says Richard Sullivan, chairman of European Cancer Research Managers Foundation and part of the EMRC team drawing up the recommendations. 'We need to know, does the benefit outweigh the toxicity?' The EMRC is pressing for a change in legislation to include this.

A change to accommodate risk-based assessment of trials is another key recommendation, which would reduce excessive insurance costs and paperwork. 'Everyone was in favour of this,' says Liselotte Højgaard, chair of the EMRC. 'Drug trials carry different risks. First drug trials are high risk whereas trials with registered drugs are lower risk.'

Getting 27 member states to iron out their different interpretations of the directive will require a lot of good will. The EMRC is calling for the heads of national authorities, medicines agencies and ethics committees to work harder on harmonising their national laws. Alongside this, they are asking for the development of new mechanisms at national and EU level for funding non-commercial trial infrastructures. Partnership and funding models were due to be developed further at the Frankfurt meeting.

'DG ENTERPRISE IS NOT CONSIDERING THE ISSUE OF SPONSORSHIP'

Harmonising the existing legislation is a key issue for the EORTC, according to its director-general Françoise Meunier. 'Each country operates differently in the same trial. This requires a change at national level as healthcare is not in the EU basket, it is reliant on national authorities. They have to speak to each other to harmonise their national legislation,' she says. 'It is particularly important for anticancer drugs, especially those developed for rare cancers as many patients are needed and trials have to be conducted multi-nationally.'

All this is taking place against the European Commission's own work. After a public consultation in 2008, it is in the process of changing the legislation on reporting adverse effects.

Ton van Lierop, spokesperson for the Commission's enterprise department in charge of the directive says 'DG Enterprise is continuously screening the clinical trials directive but is not considering the issue of sponsorship on non-commercial sponsors.'

However, the Commission's research department is funding a study on the impact of the directive on all stakeholders. The ICREL project, co-ordinated by the European Forum on Good Clinical Practice, was due to present its results in Brussels on 2 December, 2008.

Saffina Rana, Brussels

BRAF mutations 'cause resistance to therapy'

Patients with metastatic colorectal cancer whose tumours have a mutation in the *BRAF* gene do not respond to anti-EGFR therapy with cetuximab and panitumumab, European researchers say.

The finding, presented at the 20th EORTC-NCI-AACR Symposium on 'Molecular Targets and Cancer Therapeutics' (Geneva, Switzerland, 20–24th October, 2008), could help clinicians identify patients who are likely to benefit from the therapy.

Dr. Federica Di Nicolantonio (University of Turin, Italy) said that *KRAS* mutations explain about 30–40% of non-responsive cases, and the new data suggests that *BRAF* mutations may account for a further 12%. Mutations in the two genes are mutually exclusive.

Researchers conducted a genetic analysis of 113 tumours taken from patients treated with cetuximab or panitumumab. *KRAS* mutations were present in 30% cases, and were associated with resistance to the drugs. A *BRAF* V600E mutation was detected in 11 of the remaining 79 patients, representing 10% of the total number of patients.

'None of the patients with tumours containing *BRAF* mutations had responded to the treatment, and in cases where the treatment did work, none of those patients had *BRAF* mutations. This shows that for anti-EGFR therapy to work, the *BRAF* gene must be the wild type and suggests that *BRAF* status could be a useful biomarker for selecting patients suitable for anti-EGFR treatment,' Dr. Di Nicolantonio said.

Progression-free survival and overall survival was significantly shorter in patients whose tumours carried the *BRAF* mutation than in those without. In-vitro work suggested that adding the *BRAF* inhibitor sorafenib to cetuximab may increase the number of patients who could benefit from anti-EGFR therapy, but this 'remains to be assessed in a clinical trial.' She added that the research does not complete the picture: 'Further molecular markers are needed to better define patients who are unlikely to benefit from EGFR-targeted treatment.'

Molecular basis for tamoxifen resistance

The mechanism by which breast cancer therapy tamoxifen operates has been discovered by scientists at Cancer Research UK. They found that tamoxifen switches off breast cancer gene *ErbB2* via a protein called Pax2. Pax2 acts to keep *ErbB2* switched off; tamoxifen resistance occurs when *ErbB2* remains 'on' (*doi:10.1038/nature07483*).

Lead author Dr. Jason Carroll (Cambridge Research Institute, UK) said, 'We knew that women developed resistance to tamoxifen but previously our understanding of why this occurred could be compared with trying to fix a broken car without knowing how the engine worked. Now we understand how all the engine parts operate and we can try to think about ways to make repairs.

'We have discovered that for tamoxifen to work it has to block the gene *ErbB2* and it does this by using a control switch that is hidden in the background of the genome, within the *ErbB2* gene itself. In order for tamoxifen to be effective, this switch must be held in the off position by Pax2. Now we understand how women can develop tamoxifen resistance.'

Genetic susceptibility to lung cancer

Two genes which increase susceptibility to lung cancer have been pinpointed by research groups in France. The results will improve understanding of the disease, they say.

The International Agency for Research on Cancer (IARC, Lyon, France), the Centre National de Génotypage (CNG, Evry, France) and the Institut National du Cancer (Paris, France) collaborated on the largest genetic study of lung cancer ever conducted. They brought together researchers from 18 countries who investigated DNA variants in more than 15,000 people: 6000 with lung cancer and 9000 without.

The newly-located lung cancer region is on the 5th human chromosome and contains two known genes, *TERT* and *CRR9*, either of which might be the culprit (*doi: 10.1038/ng.254*). However, the researchers believe that *TERT,* which encodes part of telomerase, is the most likely candidate.

Two separate risk variants were found, and they increased life-time lung cancer risk by up to 60%, depending on the umber of copies a person carries. The risk was present in both smokers and never-smokers but the increase in risk conferred by the genes is dwarfed by that resulting from smoking.

'Rather than telling us who exactly is going to get lung cancer, these results give us a better understanding of the disease,' said Dr. Paul Brennan, head of the IARC research group. 'This will hopefully lead us to better diagnostic and treatment options.'

Standardisation of CML treatment

One year interim data from the European Treatment and Outcomes Study (EUTOS) for Chronic Myeloid Leukemia (CML) was presented at the European LeukemiaNet meeting (17–19 October, 2008, Cannes, France).

EUTOS for CML, a collaboration between European LeukemiaNet and Novartis, was initiated in October 2007. 'The goal is optimisation of treatment, and to give each patient the best possible chance of survival regardless of where they live in Europe,' said Dr. Rudiger Hehlmann (Universitat Heidelberg, Germany).

More than 2,500 patients, across 11 countries, are now entered into the EUTOS registry, including those taking first line imatinib and those already registered in existing data-bases, irrespective of treatment.

Standardisation of real-time quantitative polymerase chain reaction (RQ-PCR) – which makes it possible to compare data between centres – has been achieved in 27 out of a target of 50 laboratories across Europe with the rest scheduled for 2009. Blood tests have been analysed on 1,100 samples taken from patients suspected of not adhering to treatment, or of not responding as expected. Around 60 % had imatinib levels lower than those associated with best response to treatment.

'Quality control of molecular testing and blood testing is vital to allow us to interpret outcomes from the registry,' said Hehlmann.

PODIUM

The Stockholm Declaration

Professor Ulrik Ringborg is director of the Cancer Centre Karolinska, Stockholm. He is the former president of OECI (Organisation of European cancer Institutes); while president, he pushed through the Stockholm Declaration, signed by representatives of 17 major institutions, in November 2007. The Declaration is a pledge to work towards the creation of a collaborative platform comprised of the leading comprehensive cancer centres (CCCs) and basic/preclinical research centres in Europe.

What prompted the Stockholm Declaration?

The Eurocan+ Plus project, which was funded by the European Commission (EC) to look at how the European cancer effort could be improved, outlined a number of problems. The main one is fragmentation in research, funding and regulation which makes it difficult to develop effective translational cancer research. Fragmentation is largely caused by insufficient critical mass for carrying out complex translational research projects and clinical trials. Cancer research in Europe could be more effective. The EC acknowledged this in a Green paper in April 2007, which stated the need for infrastructures to enable Europe to be more competitive globally. We wanted to keep up the momentum for change.

How will the Declaration help?

The Declaration commits us to creating a translational cancer research platform by linking CCCs and basic and preclinical research facilities across Europe.

How exactly will the centres be linked?

Selection of centres will have to be objective and could be based on the methodology developed by the OECI for the accreditation/designation of centres: their capacity, research competences, infrastructures, quality, and so on. Selection should be peer-reviewed and flexible – over time, some centres will join and others will leave – and it must be professionally managed to stimulate excellence and generate competition.

We want to stimulate research of value for patients. The platform will promote personalised cancer medicine – meaning optimal treatment for each patient – and must open up multi-disciplinarity.

What progress has there been since the Declaration was signed?

We've had a series of meetings, most recently (15th October, 2008) at the UNESCO Headquarters in Paris supported by the Danish Cancer Society. Politicians, the European Commission, representatives of UNESCO and of patient organisations, and researchers attended the meeting. Organisations such as UICC, IAEA, IARC, patient organisations (ECPC) and the pharmaceutical industry participated. Further, representatives of ISE, EMBL, INSERM, Cancer Research UK, ESFRI, EORTC, ECCO, OECI, ECRIN, EATRIS and BBMRI were involved in the discussions. It was a constructive meeting and the platform idea was fully supported by those organisations present.

It means that we now can take a step forward, and analyse in more detail the main CCCs and basic research centres in Europe which could be included on the potential platform. It is also time to start a dialogue between the main organisations that will be responsible for coordination and integration of research centres: for example ECCO, OECI and EORTC.

Does the project depend on EC funding?

It does. We need money from Europe; there isn't another mechanism for this. UK funders won't spend money in France; similarly Swedish funders don't want to fund foreign projects. If the EC chooses to catalyse the start of this project, it would add value to money spent by each of the participating nations at home.

What would happen to European centres which aren't included?

There must be added value for centres outside the platform. A platform project on a specific tumour disease might also involve specialist teams from outside the platform. The platform must be able to collaborate with other centres. The whole concept is to stimulate European activities which improve and increase collaboration.

Is this really a paradigm shift?

It is a paradigm shift because we propose collaboration between centres and not only between research groups. This will help us to overcome the problem of a lack of critical mass relating to patients in clinical research, biological materials and competences. The necessary research infrastructures will guarantee coordination and integration of cancer research as well as the quality of education. Care of patients is increasing in complexity and if we are to identify the optimal treatment for each patient at the right time, we need molecular imaging, pathology, genomics and proteomics to find the biomarkers that allow us to stratify patients in different ways. Europe is in a unique position to develop personalised cancer medicine, provided this new collaboration between centres can be established.

Helen Saul