Transparency: An imperative in clinical research

May 21, 2014
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Landscape of randomized trials

- >1000 trials completed per month
- >30,000 patients per month
  - Median published sample size = 52

“When I had to decide whether to have a 2nd bone marrow transplant, I found there were four trials that might have answered my questions, but I was forced to make my decision without knowing the results because, although the trials had been completed some time before, they had not been properly published! I believe that research results must be seen as a public good that belongs to the community – especially patients.”

Alessandro Liberati, 2010
Half of health research is unpublished

1980 - 1996
1997 - 2005

Non-publication affects all types of trials

Song F et al, HTA 2010
Non-publication affects all types of trials


Reboxetine vs placebo

Eyding D et al. BMJ 2010

Reboxetine vs placebo

Eyding D et al. BMJ 2010
50% of trials change primary outcomes in retrospect.


50% of trials change primary outcomes

- Neurology trial
- Surgical intervention

Protocol
- Primary outcome: % with Score<3 at 1 year
- Primary outcome: % dead/dependent at 1 year

Publication
- Protocol P≥0.05
- Publication P<0.05


Evidence from regulators & litigation

- Regulatory/litigation data
- Published data

Patient morbidity and deaths

<table>
<thead>
<tr>
<th>Drug</th>
<th>Events/Year</th>
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<tbody>
<tr>
<td>Rofecoxib</td>
<td>100,000 heart attacks in 1999-2004 (US)</td>
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<tr>
<td>Lorcaïnide</td>
<td>50,000 deaths per year in 1980s (US)</td>
</tr>
</tbody>
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$$$ Billions wasted

- EU-funded health research from 1998-2006
  - €6 billion Euros $→$ 50% unpublished
    - Galsworthy MJ et al, Lancet 2012
- Gabapentin
  - $2 billion in 2002 in US $→$ 94% for off-label uses
    - Vedula S et al, NEJM 2009; Trials 2012

http://www.who.int/trialsearch
Value of trial registries

- Informed enrolment
- Track existing trials
- Transparency

Value of trial registries

- Medical & surgical trials published in top journals (2007-2012)
- Comparison of trial registries versus journal articles
- 31-49% had discrepant primary outcomes


Limitations of trial registration

- Limited methodologic information
- No universal adherence mechanism
- Variable quality of registered information
Registration of outcomes (N = 265 & 237 trials)

- Primary outcomes: 32%
- Secondary outcomes: 46%
- Adverse events: 86%


Access to protocols & full study reports

- Appraisal of study methods
- Identification of selective reporting
- Inform clinical care and future research
Current landscape

- Protocols and full study reports
  - Not publicly available
  - Variable quality
  - Variable standards

Protocols lack important information

<table>
<thead>
<tr>
<th>Information</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Allocation concealment</td>
<td>0%</td>
</tr>
<tr>
<td>Blinding</td>
<td>0%</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td>25%</td>
</tr>
<tr>
<td>Power calculation</td>
<td>40%</td>
</tr>
<tr>
<td>Harms reporting system</td>
<td>61%</td>
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</tbody>
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Benefits of sharing participant-level data

- Independent re-analysis
- Testing of secondary hypotheses
- Increased power of meta-analysis

High-profile genomic research at Duke University for lung, colon, breast, ovarian cancers (2006-9)
- Public dataset
- Led to clinical trials of personalised cancer therapy
- Fraudulent data manipulation detected by independent researchers
  - >10 journal articles retracted

Current landscape

- Data sharing remains rare
  - Even when well-accepted (genomics) or mandated
- Multiple barriers
  - Time and effort to prepare annotated data sets
  - Lack of standard guidance for best practices
Recommendation 1 – Incentives

Adopt performance metrics recognising full dissemination

- % of funded/approved studies that are published
- % of protocols, full study reports, and datasets that are made available
- Dataset re-use by external researchers

Recommendation 2 – Best practices

Develop & adopt standards for protocols, full study reports, & data sharing

- Systematic development
- Adoption by investigators, funders, sponsors, regulators, research ethics committees, journals
Recommendation 3 – Adherence mechanisms

- Endorsement and enforcement by funders, sponsors, regulators, research ethics committees, journals, legislators

Enforce study registration, access to protocols & full study reports, and data sharing for all health research
NHS Health Research Authority
- Requires registration of all UK clinical trials as condition of ethics approval

NIHR Health Technology Assessment programme
- Publishes own journal
- Withholds 10% of funds
- 98% publication rate for completed studies

New registrations per week on CT.gov

![Graph showing new registrations per week on CT.gov](chart.png)

FDAMA
FDAAA
ICMJE

100s-1000s of pages
<10 pages
100s-1000s of pages
Conclusions

- Majority of information on health research is inaccessible
- Impact on science, policy, patient care
- Action needed from key stakeholders
  - Incentives
  - Standards
  - Adherence mechanisms

What can patients do?

- Become informed
- Support transparency initiatives & legislation
- Insist on trial registration and dissemination before joining a trial