W33: ICS Core Curriculum (Free): Planning for effective and efficient clinical research and reducing the waste in incontinence research
Workshop Chair: Sakineh Hajebrahmi, Iran
15 September 2017 11:30 - 13:00

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Speaker Powerpoint Slides
Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website [www.ics.org/2017/programme](http://www.ics.org/2017/programme) Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop
This workshop is designed to provide the audience with basic and advance knowledge of methodology and terminology for clinical and biomedical research, that explore the effective and efficient biomedical research such as research priorities setting, Increasing value and reducing waste in research design, conduct, and analysis, complete or unusable reporting of biomedical research report to increase the value.

Learning Objectives
How to increase value and reduce waste when research priorities are set
Increasing value and reducing waste in incontinence research design, conduct, and analysis
Increasing value and reducing waste: addressing inaccessible incontinence research

Learning Outcomes
After the course, the audience will be able to aware of waste sources in biomedical research and they could direct they own researchs towards the best continence care.

Target Audience
Urologists, Gynecologists, Physiotherapists, Nurses or anyone who involves in clinical researches

Advanced/Basic
Advanced

Conditions for Learning
This is an interactive course but it is not restricted to small group.

Suggested Learning before Workshop Attendance
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002049

Suggested Reading
4. Buesching DP, Luce BR, Berger ML. The role of private industry in pragmatic comparative effectiveness

Other Supporting Documents, Teaching Tools, Patient Education etc

Sakineh Hajebrahimi, Sherif Mourad

Many people interested in research will go on to become authors, peer reviewers, and scientific editors of biomedical journals. However, the literature indicates that they are likely to be unprepared for any of these roles. If you’re a young researcher in the health sciences, there’s a high chance that you entered the field out of a strong desire to improve human health, directly or indirectly. Yet, according to a series published recently in The Lancet, biomedical research is doing a poor job of helping patients. Very little research ever reaches the bedside. One of the biggest reasons according to these series is waste. It has been estimated that in 2010, from nearly $240 billion invested in biomedical globally, 85% of research makes $200 billion of all the money invested in biomedical research is wasted, Few biomedical researchers really consider the needs of the patients and clinicians, and some, before starting a new project; fail to systematically review what is already known. In addition, methodological problems lead to the overestimation of the under study effect and underestimation of experimental noise, poor research protocols and study design, inappropriate use and interpretation of statistics. In all types of research and in every section of a paper, Reporting problems do show up. Inadequate descriptions of studies' contexts and objectives, cherry-picking results, and failure to report how missing data were handled are all common. A fourth article looks at inaccessible research, noting that “half of health-related studies remain unreported, and few study protocols and participant-level datasets are accessible.” A large part of the problem is selective publication—the non-reporting of negative or non-significant results—and the unwillingness of researchers to share datasets the authors write.

"The 'Planning for effective and efficient clinical research and reducing the waste in incontinence research' workshop adopts a comprehensive, evidence-based approach to the conducting research and publication process by introducing participants to the sources of waste in biomedical research. This workshop is designed to provide the audience with basic and advanced knowledge of methodology and terminology for clinical and biomedical research, and to explore the effective and efficient biomedical research such as research priorities setting, increasing value and reducing waste in research design, conduct and analysis. On the other hand, complete or usable reporting of biomedical research can increase the value. In addition, this workshop will be of interest to preclinical and clinical researchers engaged in research either as an investigator, author, peer reviewer, readers or users. The workshop will also appeal to anybody interested in the world of incontinence research and publication.

Homayoun S. Bazargani

At this session, we will focus to communicate with participants in order to improve their knowledge and skills on methodological considerations to improve the usefulness of clinical trials reducing the chance of producing research waste. Several methodological issues and misunderstandings will briefly be presented but considering the time restrictions, only issues of higher importance will be discussed with examples in the field of incontinence research. Following are the potential headings to be briefly explained through the workshop;
1- Selection of patients including sampling and eligibility.
2- Selection of the most appropriate outcomes from a variety of potential choices.
3- Criteria for selecting the primary, secondary and tertiary outcomes for clinical trials.
4- Use of scales for measuring the effect of the intervention and the validity of their use.
5- Subjective vs. objective measures of intervention effect.
6- The appropriate hypothesis type in clinical trials comparing the superiority, non-inferiority, equivalence and equality hypotheses.
7- Allocation concealment vs. blinding
8- Randomness of association vs. strength of association
9- Clinical significance margin and how to determine its size.
10- Randomization misunderstandings
11- Per-protocol vs. intention to treat analysis and dilemmas in intention to treat analysis approach in clinical trials.
12- Dosing selection choices in developing intervention protocol and standard treatment dosing.
Some examples of outcome measurement in the field of incontinence research that could be discussed or referred to through the presentation are as follows:
Outcome examples
- Change in Frequency of Urinary Incontinence, evaluating by valid questionnaire
- Improvement the quality of life
- change From Baseline in Closing Urethral Pressure
- The percent of the patients received unnecessary therapies
- The percent of completed but unpublished trials
- The percent of discontinued trials and reasons
Data collection instruments in completed trials
- Data collection instruments in the trials included: 3-day bladder diary, Urodynamics, Pad weight, Incontinence Quality of Life questionnaires, Incontinence Impact Questionnaire (IIQ-7), Uro-Genital Distress Index, SF-12 Health Survey, International Consultation on Incontinence Modular Questionnaire Urinary Incontinence Short Form (ICIQ-Ul SF), International Consultation on Incontinence Modular Questionnaire Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol)

**Sajjad Rahnama'i**

Addressing inaccessible research
We will discuss the issue of research accessibility from four various aspects
1. Factors related to the clinician or person looking for available evidence
   a. The limitations basic computer and web use skills
   b. The limitations in knowledge about the variety of available literature search resources
   c. Language capabilities to access research
   d. Lack of enough skill in forming an appropriate search strategy or use search engines
   e. Limited access to skilled librarians and ability to transfer the clinicians need for help explained to the librarians.
2. Factors related to potential evidence producers
   A: Weak intention to disseminate research findings and scientific information due to legal, social and political reasons
   B: Weak intention to disseminate research findings and scientific information due to low motivation (such as in health systems)
   C: Lack intention to fully disseminate research findings and scientific information due to potential conflict of interests.
   D: lack of enough skill in scientific writing or language limits
3. Factors related to the content of evidence and research to be accessible
   A: Quality of reporting affects full accessibility to produced research findings
   B: The issue of gray literature and publication likelihood
   C: Limited indexing and archiving of published research reports for various reasons.
   D: Unstandardized web-publishing not using the recent advances in this field (SEO) which leads to lower likelihood of the published being discovered form among the gigantic mass of information in internet
4. Factors related to information retrieval resources including scientific databases
   A: Economical limitations in access to purchasable research findings or access to commercial scientific databases that include many valuable research findings
   B: The coverage rate limitation of the available literature databases
   C: Technologic limitations and capabilities of search engines to ensue efficient search in literature
   D: Existence of field-specific databases in incontinence science. There are such databases in other areas such as AIDS line, safety lit, etc.

**Sakineh Hajebrahmi**

Several avoidable reasons show that roughly 85% of healthcare research funding may be wasted, including poor research question selection, poor study design, selective non-publication and poor reporting. All actors in the research field—researchers, institutions, regulators, funders, publishers, and policy makers—have important roles in waste reduction. To reduce waste from poor reporting, many high-impact medical journals endorse and actively implement reporting guidelines that specify a minimum set of items required for a clear and transparent account of what was done and what was found in the study. For specific types of research, Over 300 reporting guidelines have so far been published. Key reporting guidelines include the CONSORT statement for randomized controlled trials, the STROBE statement for observational studies, the STARD statement for diagnostic accuracy studies, and the PRISMA statement for systematic reviews.

To improve poor reporting, it is necessary to provide more opportunities to researchers and reviewers (and even editors) to learn reporting guidelines. Which questions were addressed and why, what was done, what was shown, and what the findings mean is what adequate reports of research should clearly describe. However, substantial failures occur in each of these elements. The need to reduce waste and add value is pressing in low-income and middle-income countries. Surely, aligning their research with their public health and development needs is what such countries would benefit from. Even for clinical trials, research done in low-income and middle-income countries often pertains to diseases more relevant to wealthy nations. Current workshop is held to talk about reporting guidelines. In addition to teach to the researchers the effectively write, publish, and disseminate research. Researchers, reviewers, and editors will benefit from participating in this workshop, which might contribute to waste reduction in research. Similar efforts should be made in entire international continence societies to provide learning opportunities for reporting guidelines.
A first step towards increasing the value and reducing research waste is monitoring the problems and develop solutions that aim to fix them. Randomized controlled trials are the gold standard tool for evaluating interventions. Nevertheless, the utility of this excellent tool is contingent on how it is used.

As real examples: out of 1088 studies in the field of urinary incontinence that were registered in ClinicalTrials.gov, 881 trials were relevant to urinary incontinence interventional methods. From these, 117 studies were completed with results and 339 studies were without results. However, according to our primary search results, from pubmed.gov, 3045 clinical trial studies on human were reported. It shows that many trials are entirely lost, as they are not even registered. Moreover, most of journal editors not requested or encouraged trial registration.

Urinary incontinence is defined as involuntary loss of urine, such as leaking of urine. It is a symptom of various underlying pathological processes. Major types of incontinence include urinary urge and stress incontinence. These patients can be classified as uncomplicated or complicated.

The positive result of any screening test should be dealt with in the same way as a presenting symptom, by carefully considering its evidence based differential diagnosis.

In completed trials registered in ClinicalTrials.gov, there are different definition of eligible criteria for patients with urinary incontinence: in some studies it classified as have a ≥ 3 month history of experiencing Stress Urinary Incontinence (SUI) per week (self-reported); while in another it considered as urge or stress urinary incontinence at least twice a week on average for at least 3 months. However in others it confirmed with urodynamics.
Planning for: effective and efficient clinical research and reducing the waste in incontinence research

Chair: Sakineh Hajebrahimi, MD, Professor of Urology, Tabriz University of Medical Sciences, Tabriz, Iran

Speakers:
- Sherif Mourad, Professor of Urology, Egypt
- Homayoun Sadeghibazargani, Associate professor of Epidemiology, Karolinska Institutet, Sweden
- M. Sajad Rahnama'i, Urologist and senior Researcher from Maastricht University in the Netherlands

**NEW FOR 2017**
Please complete the in-app evaluation in the workshop before leaving.

- A shortened version of the handout has been provided on entrance to the hall
- A full handout for all workshops is available via the ICS website.
- Please silence all mobile phones
- Please refrain from taking video and pictures of the speakers and their slides. PDF versions of the slides (where approved) will be made available after the meeting via the ICS website.

Tabriz University of Medical Sciences, Tabriz, Iran
Ice breaking!

Are you a researcher?

Are you a research results utilizer/user?

BOTH???

Majority of medical researched are useful and well directed?

1. TOTALLY AGREE
2. Agree
3. No comment
4. Disagree
5. Totally disagree

Insufficient data???

Mismatch between what clinical researchers do and what patients need

Type of research (categories included)

<table>
<thead>
<tr>
<th>Type of research</th>
<th>2004/5</th>
<th>2009/10</th>
</tr>
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<tbody>
<tr>
<td>Pure basic (aetiology and underpinning)</td>
<td>68.3</td>
<td>59.4</td>
</tr>
<tr>
<td>Pure applied (prevention, detection &amp; diagnosis, treatment evaluation, disease management, health services)</td>
<td>21.2</td>
<td>27.2</td>
</tr>
<tr>
<td>Use-led basic (development of detection, diagnosis and treatment)</td>
<td>10.7</td>
<td>13.3</td>
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Promising ideas developed in basic research were not being translated into applied research; they were meeting a bottleneck in assessments of whether they could lead to advances in prevention and treatment.

Low priority questions addressed in research on treatments for osteoarthritis of the knee

- Knee replacement
- Education and advice
- Drugs
- Complementary therapy
- Physical therapies
- Miscellaneous others


Waste in research

Questions relevant to clinicians & patients?

- Low priority questions addressed
- Important outcomes assessed
- Clinicians and patients involved in setting research agendas

Unbiased and usable report?

Adopted from Lancet Series on Waste in research, with permission of Paul Glasziou

Waste at four stages of research

Questions relevant to clinicians & patients?

- Low priority questions addressed
- Important outcomes assessed
- Clinicians and patients involved in setting research agendas

Appropriate design and methods?

- Studies take adequate steps to reduce biases
- Randomized treatment allocation

Accessible full publication?

- Studies published in full
- Efficient delivery of research
- Reporting of studies with disappointing results

Unbiased and usable report?

85% Research waste = over $100 Billion / year

Paul Glasziou and Iain Chalmers

Avoidable waste in the production and reporting of research evidence

- High priority questions addressed
- Important outcomes assessed
- Clinicians and patients involved in setting research agendas

Appropriate research design, conduct and analysis?

- Studies take adequate steps to reduce biases
- Randomized treatment allocation

Efficient research regulation and delivery?

- Good use of data

Accessible full research reports?

- Studies published in full
- Efficient delivery of research
- Reporting of studies with disappointing results

Unbiased and usable reports?

Adding value in research framework

- Trial interventions sufficiently described
- Reporting planned study outcomes
- New research interpreted in context of systematic assessment of relevant evidence
1. Setting research priorities

The inefficiency of basic science research

- 1 intervention used widely
- 5 resulted in licensed clinical interventions by 2003
- 101 claimed that new discoveries had clear clinical potential
- >25,000 reports in 6 basic science journals 1979-83

Incontinence publication in Pubmed

- 39990 evidence for urinary incontinence research
  - 35580 human
  - 1820 animals,
  - 1332 SR or meta,
    - Surgical 18123
    - Non surgical 1129
    - 1764 RCT,

  *119 guideline!

1. Setting research priorities

Set research in the context of systematic reviews

<table>
<thead>
<tr>
<th></th>
<th>May 2009 (n=29)</th>
<th>May 2012 (n=32)</th>
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<tbody>
<tr>
<td>Claims that clinical trial is the first to address the question</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Contains an updated systematic review that was used to inform trial design</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Previous systematic review* discussed that was not used in trial design</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Contains references to other randomised trials</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Does not contain references to other randomised trials or claims to be the first trial</td>
<td>9</td>
<td>6</td>
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Table 2: Analysis of Introduction sections of reports of controlled trials published in five medical journals in May, 2009, and May, 2012

From 16 almost 2 referred the SR.
Unclear and different out comes and measurements
Referenced the previous RCT in half of Medical Intervention in OAB

2. Design, conduct and analysis

High effect-to-bias ratio

- Blinded assessment of outcome
- Conflicts of interest statement
- Randomisation

In vivo studies
3. Regulation and management

Better recruitment after UK clinical research networks

- Participants recruited into observational studies
- Participants recruited into interventional studies

4. Accessible reporting

Proportion of funded/completed research that is reported

50%

4. Accessible reporting

Associations with reporting

- USA or Canada and other: 2010-2013
- UK or Canada: 2010-2013
- USA: 2010-2013
- Others: 2010-2013
- N=60

5. Complete & usable reporting

Poor reporting in publications: range of 24% to 89% “missing”

Abstract

- 38%, 49%

Methods

- 40-89%, 33%, 65%, 31%

Results

- 50%, 65%, 54%, 92%, 24%, 40%

Discussion

- 50%

Data

- Almost all
Research question relevant to users?
Appropriate research design?
Efficient research regulation, and delivery?
Accessible full report?
Unbiased and usable report?

Open Access

Research Production

Research Dissemination

Users aware?
Users agree?
Users able to apply?
Users adopt?

Thank you
Addressing Inaccessible Research

What is inaccessible research?

Research data that are not published.
Research data that are only partly published.
Research data that are hard or impossible to access.

Alessandro Liberati

Italian healthcare researcher and clinical epidemiologist

Founder of the Italian Cochrane Centre.

In 2010, Alessandro Liberati explained the difficulties he encountered when he had to make decisions about his treatment for multiple myeloma:

“When I had to decide whether to have a second bone-marrow transplant, I found there were 4 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....”

He believed that within a health system, research should be an integral part of its mission, especially where lack of commercial interests prevents the possibility of private investment.

Researchers should concentrate on what is relevant to patients, not to their careers or to drug companies.

Moreover, he strongly believed that developing alliances with consumers is necessary for setting research priorities, and that research results should be easily accessible to people who need to make decisions about their own health.
**Alessandro Liberati**

“I believe that research results must be seen as a public good that belongs to the community; especially patients.”

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**BIAS**

Defined as any tendency which prevents unprejudiced consideration of a question.

In research, bias occurs when “systematic error [is] introduced into sampling or testing by selecting or encouraging one outcome or answer over others”

Bias can occur at any phase of research, including study design or data collection, as well as in the process of data analysis and publication.

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**Scientific literature represents an incomplete and biased subset of research findings.**

For example, when unreported trials were included in a meta-analysis, **Reboxetine** was shown to be more harmful & no more efficacious than placebo for treatment of major depression

— a different finding from that when only reported trials were included!
Rosiglitazone

- Not reported part of data:
  Unfavourable trials and sponsor's meta-analysis not reported
  Increased risk of myocardial infarction confirmed by independent meta-analysis of 56 rosiglitazone trials, which included 36 unreported trials for which data were obtained from the sponsor's trial Registry

- Effects
  Number needed to harm of 37–52 for 5 years translates into 6000–8000 additional myocardial infarctions in 325 000 patients taking rosiglitazone in the USA and UK in 2010
  About 83 000 additional myocardial infarctions potentially attributable to rosiglitazone in the USA from 1999 to 2006

Celecoxib

- Selective reporting
  Only favourable 6-month harms data in trial report, with suppression of unfavourable 12–15-month data that no longer showed benefit for reduction of gastrointestinal ulcers.
  Discrepant reporting of cardiovascular mortality data between regulatory report and two published reports of the same trial

- Effects
  In 2004, 600 000 users in the UK and more than 14 million prescriptions filled in the USA for an expensive drug with questionable benefit rather than cheaper alternatives

Ezetimibe–Simvastatin

- Delayed reporting
  Report of randomised trial showing no benefit of Ezetimibe–Simvastatin vs simvastatin alone delayed by 2 years!

Selective reporting of positive preclinical or observational research

- Reported results of only 11–25% of promising preclinical studies can be independently replicated for drug development.
- Clinical trials often do not confirm the benefit shown in previous reports of animal or clinical studies.
- Inaccessible research can lead to redundant, misguided, or potentially harmful research assessing similar interventions.

Grey Literature
Grey Literature

Defined as materials and research produced by organisations outside of the traditional commercial or academic channels.

e.g.
Reports, government documents, evaluations etc

Access

Even when studies are reported, access to research reports is restricted.

Journal subscriptions are costly, particularly in low-income settings, but even for leading private academic institutions.

Although the number of open-access reports has been increasing,

But still, access to 78% of reported medical research was restricted to journal subscribers in 2009.

Language barriers

Most high profile scientific journals are published in English, but much of the scientific literature is in other languages.

More than 2500 biomedical journals are published in Chinese, fewer than 6% of which are indexed in Medline.

Publications in languages other than English are often excluded from systematic reviews because of inaccessibility or limited resources for translation and searching.

http://sci-hub.bz/

Conclusions

Majority of information on health research is inaccessible

Impact on science, policy, patient care

Action needed from key stakeholders
Incentives
Standards
Adherence mechanisms

Addressing Inaccessible Research

Maastricht University Medical Centre, The Netherlands

Sajjad Rahnama’i, MD. PhD. FEBU.
**INCREASING VALUE AND REDUCING WASTE IN RESEARCH DESIGN, CONDUCT, AND ANALYSIS**

Homayoun Sadeghi-Bazargani MD, PhD  
Clinical Epidemiologist  
WHO Collaboration Center on Community Safety Promotion, PHS Department, Karolinska Institute, Sweden  
Swedish Science Pioneers, Stockholm, Sweden  
Clinical effectiveness department, Iranian center for evidence based medicine, Tabriz, Iran

Lecture sponsored by: ICS

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**Waste at four stages of research**

- **Questions relevant to clinicians & patients?**
- **Appropriate design and methods?**
- **Accessible full publication?**
- **Unbiased and usable report?**

85% Research waste = over $100 Billion / year

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**Relevant reproducible protocol**

Think of details and provide them in your research protocol before your study.

Consider variabilities regarding intervention implementers i.e. experience of surgeons, educators,  
Consider variabilities in materials used in intervention such as producer, drug forms, ....

Consider variabilities in timing  
Take care of dose variabilities for efficacy

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**Relevant reproducible intervention protocol**

- **Solifenacin:** 5-10mg  
- **Tolterodine:** 2-4 mg

**Study A:** Solifenacin 10 mg vs. Tolterodine 2 mg

**Study B:** Solifenacin 5 mg vs. Tolterodine 4 mg
Outcome

It should be:
Well defined
Unbiased
Stable
Reproducible
Valid and reliable scales for subjective outcomes
Ascertainable in all participants
Adequately address study hypothesis

Are you annoyed with your incontinence?
1- Yes   2- No

Treatment with Drug A was more effective than Drug B (P<0.05)

Scale development

Do not just put few questions based on your own experience and start your clinical trial.
Measuring is science itself!

Follow the standards of scale development if you need a new one.

Translation or adaptation

I have done my fellowship on incontinence in US and my English is good. I will translate it and use it in my clinical trial.

There are standards for translation and adaptation of scales. Follow them or ask someone to do it before starting your clinical trial.

You may have even higher chance for publishing your scale translation than to publish your clinical trial!
Measure, analyze and report both on safety and effect.

Measuring only the efficacy not thinking of safety may lead to waste

Do we have to think of safety at all the 4 clinical trial phases?

Statistical power and sample size

Ethics of inappropriately small or large sample sizes

Compensation by systematic reviews?

Watch your conclusion especially for insignificant results

Solifenacin and tolterodine are equally effective in the treatment of overactive bladder symptoms.

At week 12, solifenacin and tolterodine demonstrated equal efficacy in reducing the number of micturition (-0.58 ± 1.31 vs. -0.60 ± 1.56, p = 0.58), urgency (-0.76 ± 1.87 vs. -1.13 ± 2.38, p = 0.37) and incontinence (0.79 ± 2.92 vs. -0.61 ± 2.31, p = 0.28) episodes per 24 hours.

Statistical power: ?

The highest power (but not adequate) belonged to constipation/12.8% in Sol, 2.8% in Tol.

The major limitation of the present study, in comparison with previous studies in western countries, was the relatively small patient number. This could have decreased the power for detecting a difference between the two medications. However, the present study is still valuable in providing experience in the use of both drugs in a Taiwanese population, which has been rarely reported before.

Conclusion: Both solifenacin and tolterodine are effective in treating key OAB symptoms, including urinary frequency, urgency and incontinence in the Taiwanese population. Both medications are comparably effective and safe, with the most common adverse effects being dry mouth and constipation.

If I was the author: We can't conclude. Others should do it using our results in metaanalysis.

Types of hypotheses?

High effect-to-bias ratio

Think of clinical trial biases before starting your study

High effect-to-harm assessment/reporting ratio

Comparing Treatments

• Fundamental principle
  • Groups must be alike in all important aspects that may have an effect on continence symptoms or development of unwanted conditions
  • Only differ in the intervention each group receives
  • In practical terms, “comparable treatment groups” means “alike on the average”

• Randomization
  • Each participant has the same chance of receiving any of the interventions under study
  • Allocation is carried out using a chance mechanism so that neither the participant nor the investigator will know in advance which will be assigned

• Blinding
  • Avoidance of conscious or subconscious influence
  • Fair evaluation of outcomes

A bias is a systematic error, or deviation from the truth, in results or inferences. Different biases can lead to underestimation or overestimation of the true intervention effect. Biases can vary in magnitude
Selection bias refers to systematic differences between baseline characteristics of the groups that are compared.

The unique strength of randomization is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants.

Randomization is a process through which study subjects are assigned to different trial interventions or treatments only by chance.

**RANDOM SEQUENCE GENERATION**

**'Low risk' of bias**
- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimization.

**'High risk' of bias**
- The investigators describe a non-random component in the sequence generation process. For example:
  - Sequence generated by odd or even date of birth;
  - Sequence generated by some rule based on date (or day) of admission;
  - Sequence generated by some rule based on hospital or clinic record number.
  - Allocation by judgement of the clinician;
  - Allocation by preference of the participant;
  - Allocation based on the results of a laboratory test or a series of tests;
  - Allocation by availability of the intervention.

**Allocation sequence concealment**

**'Low risk' of bias**
- Participants and investigators enrolling participants could not foresee assignment
- Central allocation (including telephone, web-based and pharmacy-controlled randomization);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

**'High risk' of bias**
- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.
Performance bias

Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.

After enrolment into the study, blinding (or masking) of study participants and personnel may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcomes.

Placebo example

BLINDING OF PARTICIPANTS AND PERSONNEL

Low risk
Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;

‘High risk’
No blinding or incomplete blinding, but the review authors judge that the outcome is likely to be influenced by lack of blinding;

Detection bias

Detection bias refers to systematic differences between groups in how outcomes are determined. Blinding (or masking) of outcome assessors may reduce the risk that knowledge of which intervention was received, rather than the intervention itself, affects outcome measurement. Blinding of outcome assessors can be especially important for assessment of subjective outcomes, such as degree of postoperative pain.

Attrition bias

Attrition refers to situations in which outcome data are not available.

Attrition bias refers to systematic differences between groups in withdrawals from a study. Withdrawals from the study lead to incomplete outcome data.
INCOMPLETE OUTCOME DATA

Low risk
No missing outcome data;
Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
Missing data have been imputed using appropriate methods.

INCOMPLETE OUTCOME DATA

High risk
Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomization;
Potentially inappropriate application of simple imputation.

Reporting bias
Reporting bias refers to systematic differences between reported and unreported findings.
Within a published report those analyses with statistically significant differences between intervention groups are more likely to be reported than non-significant differences.
This sort of ‘within-study publication bias’ is usually known as outcome reporting bias or selective reporting bias, and may be one of the most substantial biases affecting results from individual studies.

Danger of overvaluing p values. Effect size
Danger of multiple p values not corrected for multiple test
Association of the Gene X expression with incontinence- a microarray study

One reason for the need to define primary outcome

There are other reasons either: Apriori-ness, Design tailoring

Thanks for your attention

Thanks to ICS

Any questions?
Ask now or send me an email
homayoun.sadeghi@swedensp.se
Planning for: effective and efficient clinical research and reducing the waste in incontinence research, good reporting

Sakineh Hajebrahimi, MD, Professor of Urology, Tabriz University of Medical Sciences, Tabriz, Iran

Research aim:
A Survey on the Abundance of Adherence to STARD and CONSORT Standards in the Abstracts of Diagnostic Accuracy Studies and Randomized Controlled Trials Published in International Controversy Society Abstract Book, 2015

Table 1: Analysis of Adherence of STARD to CONSORT Checklists

<table>
<thead>
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<th>Item</th>
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<tr>
<td>Total</td>
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</tbody>
</table>

Research: increasing value, reducing waste 5

Reducing waste from incomplete or unusable reports of biomedical research

Paul Glazier, Danielle Attia, Patric Boult, Isabel Burton, Mike Clarke, Debra Duvall, Sean Elms, David Wyles, Elizabeth Wager

Good Reporting of Clinical Trials

Austin Bradford Hill, 1965

Four questions to which readers want answers when reading reports of research.
1. Why did you start?
2. What did you do?
3. What answer did you get?
4. And what does it mean anyway?
"Young man, why would I feel like a failure? And why would I ever give up? I now know definitively over 2,000 ways that an electric light bulb will not work. Success is almost in my grasp.”

Thomas Edison

Avoidable waste = no or inadequate records of what has failed.

Unavoidable “waste” in research

Adequacy of treatment descriptions in 80 studies reporting beneficial treatments

- Description sufficient to replicate
- Overall: 0%, Drug: 10%, Non-drug: 0%

Glasziou et al BMJ, 2008

Many problems are fixable

Adequacy of treatment descriptions in 80 studies reporting beneficial treatments

- Description sufficient to replicate
- Overall: 0%, Drug: 10%, Non-drug: 0%

Glasziou et al BMJ, 2008

Reporting = paper + protocol + materials + data + … + links


Details of fMRI methods in 241 studies

Comments on News Item

Q1: “... would make the paper quite inaccessible if every detail were published.”
A: use a “supplementary information” system, posted online

Q2: “... contacting the author directly would provide a lot of the necessary information.”
A: “I’ve gotten about a 10% response rate. Sometimes the authors of studies have died or moved out of the field and the information is lost forever.”

Carp J. The secret lives of experiments: Methods reporting in the fMRI literature. NeuroImage, 2012, 63 (1), 299-300

About 7% permanent loss / year

- Of 516 papers on morphological data from plants, animals, or other organisms
- For 2011, 37% data available
- For 2001, 18%
- For 1991, 7%

Reporting = paper + protocol + materials + data + ... + links

Austin Bradford Hill, 1965

Four questions to which readers want answers when reading reports of research.
1. Why did you start?
2. What did you do?
3. What answer did you get?
4. And what does it mean anyway?

Abstract
38%, 49%

Methods
40-89%, 33% 65%, 31%

Results
50%, 65%, 54%, 92%, 24%, 40%

Discussion
50%

Data
Almost all

Poor reporting in publications: range of 24% to 89% “missing”

Abstract
Title: estimating effect size and confidence interval (95%), no mention of adverse effects (4%)?

Methods
Trials: 65-80%, inadequate treatment description\textsuperscript{11} 30% MRI studies: 33%, missing number of trials and duration\textsuperscript{20}
Survey questions: 33% missing survey or comparison\textsuperscript{18} Figures: 35% graphs uninterpretable\textsuperscript{16}

Results
Clinical trials: outcomes missing: 50% efficacy and 65% have outcomes per trial incompletely reported.
Animal studies: number of animals and use of data missing\textsuperscript{14} (54%, 52%) age and weight missing (24%)Diagnostic studies: missing age and sex (28%)\textsuperscript{14}

Discussion
Trials: no systematic attempt to set new results in context of previous trials (59%)\textsuperscript{17}

Data
Trials: most data were made available; author held data but at about 2% per year

All trials registered
All results reported

House of Commons
Committee of Public Accounts
Access to clinical trial information and the stockpiling of Tamiflu

Recommendation: The Department and the MIHRA should ensure, both prospectively and retrospectively, that clinical trials are registered on an appropriate registry and that the full methods and results of all trials should be available for wider independent scrutiny, beyond the work undertaken by regulators during the licensing process.

All results methods & materials

House of Commons
Committee of Public Accounts
Access to clinical trial information and the stockpiling of Tamiflu

Recommendation: The Department and the MIHRA should ensure, both prospectively and retrospectively, that clinical trials are registered on an appropriate registry and that the full methods and results of all trials should be available for wider independent scrutiny, beyond the work undertaken by regulators during the licensing process.

Our Recommendations

Motive
Means
Opportunity

Michie et al. Implementation Science 2011, 6:42

Recommendation 2: Infrastructure

Research funders should take responsibility for reporting infrastructure that supports good reporting and archiving

In the future: “Whether the full protocol should be submitted...”
3085 incontinence research proposals that registered in clinicaltrial.gov:

- Complete 387 (with or without submission of results)
- Recruiting: 123
- Enrolment by invitation: 13
- Suspended: 1
- Active not recruiting: 31
- Terminated: 43
- Withdrawn: 78
- Unknown: 

Recommendation 3: Capacity

Funders, institutions, and publishers should improve the capability and capacity of authors and reviewers in high-quality and complete reporting.

INTERNATIONAL STANDARDS FOR CLINICAL RESEARCH

International, explicit, rules-based methods exist for all aspects of clinical trial implementation & reporting.

INTERNATIONAL STANDARDS FOR CLINICAL RESEARCH

hypothesis formulation
literature searching, literature review
ethical review
trial planning, trial conduct
trial reporting
systematic review
meta-analysis

AGREE STATEMENT
www.agreecollaboration.org/
Clinical practice guidelines assessment

ASSERT STATEMENT
www.assert-statement.org/
Ethical review of clinical trial proposals and monitoring Randomized controlled trial conduct and reporting

COCHRANE COLLABORATION
www.cochrane.org
Systematic reviews of randomized controlled clinical trials

NICE STATEMENT
www.nice.org.uk
Technology appraisal of clinical guidelines National Institute for Clinical Excellence

QUOROM – CONSORT STATEMENT
www.consort-statement.org/QUOROM.pdf
Meta analysis of randomized controlled trials conduct and reporting

CDISC
http://www.cdisc.org
CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

DUET STATEMENT
www.duets.nhs.uk
The Database of Uncertainties about the Effects of Treatments

MOOSE – CONSORT STATEMENT
www.consort-statement.org/MOOSE.pdf
Meta analysis of observational trials conduct and reporting
International standards for clinical research

SDTM: STANDARDS-BASED CLINICAL TRIAL DATA MANAGEMENT (based on CDISC)

STARD - CONSORT STATEMENT
www.consort-statement.org/stardstatement.htm

DIAGNOSTIC TRIALS CONDUCT & REPORTING

STROBE STATEMENT
http://www.strobe-statement.org/
Strengthening the Reporting of Observational studies in Epidemiology

TREND STATEMENT
http://www.trend-statement.org/
Transparent Reporting of Evaluations with Nonrandomized Designs

improves the reporting standards of nonrandomized evaluations of behavioral and public health interventions

The Recommendations

1. Funders and research institutions must shift the research regulations & rewards to align with better & more complete reporting
2. Research funders should take responsibility for reporting infrastructure that supports good reporting and archiving
3. Funders, institutions, and publishers should improve the capability and capacity of authors and reviewers in high-quality and complete reporting

Thank you