Cognitive biases, errors, and questionable research practices with a focus on clinician-researchers or clinical research in general
Outline

The current clinical research (trial) landscape
- Some issues with quality
- Our current academic reward system

Being a researcher
- (Cognitive) biases
- Human errors
- Research misconduct
- Questionable research practices

Possible solutions for clinical research
Disclosure

Biases and conflicts of interests
My biases

with regard to the topic of this talk

- Not (so) young anymore (you can usually guess age by the level of logorrhea – so I feel very old …)
- I am male
- Father of two kids in an age where they can stay at home alone even in the evening
- Settled in Schmitten, FR
- I have an unlimited contract at the University of Bern
- Well-established professional network
- I am trained as physician but I am actually a methodologist
My conflict(s) of interests

- CTU Bern depends on clients and people who seek help
- The more I stress specialization and expertise the better
- The more I downplay the role of the clinician-researcher the better for us
Am I qualified?
to talk about this topic
Am I qualified?

My academic career

.average-talented (so far, nobody was honest/courageous enough to tell me, therefore: a self-reflection)

. I applied three times for a professorship (at least one serious application), all unsuccessful (including one in Bern)

+ I work in academia for 15 years now (3 years in a clinical department)

+ I have consulted on >500 clinical research projects, >50 grant applications, and have peer reviewed many
A warning at the beginning
The clinical research (trial) landscape
Clinical trials approved by Swissmedic
Pharmaceutical products and devices

Graph showing the number of approved trials over the years 2009 to 2017, with a downward trend.
Global clinical trials
Clinical trials published in MEDLINE
Completeness of 113 approved protocols by Swiss ethics committees 2010-12

- Title
- Table of contents/index
- Funding source for the complete study
- Background and rationale
- Objectives or hypothesis
- Trial or study design
- Trial or study setting
- Intervention/s
- Outcome or endpoint/s measures
- Sample size
- Randomization or assignment of intervention
- Statistical methods
- Safety or harms
- Ethical consideration
- Data protection
- Confidentiality
- Access to data
- Dissemination policy

Weidmann R 2018
Concordance protocol-registry

113 approved protocols

Assessment

Five domains (inclusion and exclusion criteria, intervention, sample size, primary outcome)

- **Concordant**
- **Protocol contains more information**
- **Registry contains more information**
- **non Alignment between the two**

Weidmann R 2018
Discrepant reporting of outcomes

Cohort of Swiss clinical trials

- Omission from publication (non-reporting)
- Addition of an outcome
- Change from primary to secondary (or vice versa)

- 452 protocols approved by Swiss ethics committees (1988-98) screened
- 227 with at least 1 publication
- 333 publications used to extract outcomes (comparison with protocol)

Redmond S et al. 2013
Extend of discrepant reporting

<table>
<thead>
<tr>
<th>Outcomes defined in protocols as</th>
<th>Classification(^a)</th>
<th>(N)</th>
<th>Prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting in published article</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Concordant (1-1)</td>
<td>165</td>
<td>60.2% (54.2, 66.1)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Discrepant (1-2)</td>
<td>90</td>
<td>32.8% (27.3, 38.8)</td>
</tr>
<tr>
<td>Not reported</td>
<td>Discrepant (1-0)</td>
<td>19</td>
<td>6.9% (4.2, 10.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes reported in publications as</th>
<th>Classification(^a)</th>
<th>(N)</th>
<th>Prevalence (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Definition in study protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Concordant (1-1)</td>
<td>175</td>
<td>60.8% (54.9, 66.4)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Discrepant (2-1)</td>
<td>83</td>
<td>28.8% (23.7, 34.4)</td>
</tr>
<tr>
<td>Not defined</td>
<td>Discrepant (0-1)</td>
<td>30</td>
<td>10.4% (7.1, 14.5)</td>
</tr>
</tbody>
</table>

Redmond S et al. 2013
Tracking switched outcomes in clinical trials

Outcome switching in clinical trials is a serious problem. Between October 2015 and January 2016, the COMPare team systematically checked every trial published in the top five medical journals, to see if they misreported their findings:

1. We compared each clinical trial report with its protocol or registry entry. Some trials reported their outcomes perfectly. For the others, we counted how many of the outcomes pre-specified in the protocol or registry were never reported. We also counted how many new outcomes were silently added.

2. When we detected unreported or added outcomes, we wrote a letter to the journal pointing them out. We tracked which journals published our letters – and which did not.

Here's what we found.

<table>
<thead>
<tr>
<th>Trials Checked</th>
<th>Trials Were Perfect</th>
<th>Outcomes Not Reported</th>
<th>New Outcomes Silently Added</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td>9</td>
<td>300</td>
<td>357</td>
</tr>
</tbody>
</table>

On average, each trial reported just 62.1% of its specified outcomes. And on average, each trial silently added 5.3 new outcomes.
Our (rotten?) academic reward system

- Research assessment exercise in Bern (up to 2017*)/habilitation
  - (Only) Articles published in high-impact journals are valued
  - (Only) first and last authorship really counts
  - Content and quality per se does not matter**
  - True collaboration is not valued (as their is no easy indicator?)
- Individual achievements count and ruthlessness is not a bad idea
- Ownership versus openness

* Although it has changed it is still in our minds and culture (only personal experience, though)

** I have nothing against quantitative indicators but they need to be sensible and appropriately interpreted (knowing what exactly they measure and their limitations)
A possible consequence

A recent example (N Engl Med 2018; 379: 1313-21)
... The trial was sponsored by Bristol-Myers Squibb, which designed the trial, provided the trial drug and placebo, conducted blinded safety monitoring, developed the analysis plan, analyzed the results, and funded professional writing assistance. A contract research organization (ICON, Dublin) conducted the trial under the direction of the sponsor, and medical writers paid by the sponsor wrote the first draft of the manuscript. All the authors had full access to the trial data, reviewed and approved the manuscript before submission, and vouch for the adherence of the trial to the protocol, the completeness and accuracy of the data and analyses, and the reporting of adverse events. There were confidentiality agreements between the authors and the sponsor.
International Committee of Medical Journal Editors authorship criteria

– Substantial contributions to conception and design, or acquisition of data, or analysis, or interpretation of data
– AND drafting the article or revising it critically for important intellectual content
– AND final approval of the version to be published
– AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved
Let's remind us of the list of authors
Non-industry authors yellow

And where are the ICON people?
The author?
The other people from BMS?
The people that actually worked with participants at the study sites...
Being a researcher
characteristics good researcher

www.google.com

- 5 Qualities of a Good Researcher
  - manifests thirst for new information
  - keen sense of things around him
  - likes to reflect or think about the things he (sic!) encounters
  - must be intelligent enough to express his (sic!) ideas
  - applies a systematic approach in assessing situations

- (sic!) → implicitly: must be a male

https://simplyeducate.me/2012/10/24/5-qualities-of-a-good-researcher/
Good ≠ Success
What do I think makes a good researcher?

Not necessarily a successful, though!
Cognitive biases

www.yourbias.is & www.yourlogicalfallacies.com

- Bystander effect
  - Someone else will take care …

- Framing
  - Undue influenced by context and delivery

- Availability heuristic
  - Undue influenced of what springs most easily to mind
Human errors
A particular type of error

What they are not

- Not incompetence  → Training!
- Not misunderstanding  → Communication!
Human errors

A particular type of error

Types

- Random errors
  → Risk assessment
  → Quality Control?

- Systematic errors
  → Quality assurance:
    Screen – analyze – change
Research misconduct

FFP

- Fabrication
- Falsification
- Plagiarism
Fabrication and falsification

– … a significant effect was found for surveys targeted at medical and clinical researchers, who reported higher percentages of misconduct than respondents in biomedical research and other fields.

Fanelli D 2009; Fiedler 2015
Questionable research practices

To mention a few

- Sloppiness
- Failure to follow protocol
- Over-interpretation of results
- Failure to publish, selective reporting
- Conflicts of interest
- ...

George SL 2016; John 2012
Annals of Internal Medicine

N=400 (of 522) ASA statisticians

Wang 2018
<table>
<thead>
<tr>
<th>Violation Request</th>
<th>Respondents Rating the Item as “Most Severe,” %</th>
<th>Reported Requests During the Past 5 Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falsify the statistical significance (such as the P value) to support a desired result</td>
<td>84</td>
<td>97, 2, 1</td>
</tr>
<tr>
<td>Change data to achieve the desired outcome (such as the prevalence rate of cancer or another disease)</td>
<td>84</td>
<td>93, 7, 1</td>
</tr>
<tr>
<td>Remove or alter some data records (observations) to better support the research hypothesis</td>
<td>80</td>
<td>76, 22, -</td>
</tr>
<tr>
<td>Interpret the statistical findings on the basis of expectations, not the actual results</td>
<td>68</td>
<td>70, 28, 2</td>
</tr>
<tr>
<td>Do not fully describe the treatment under study because protocol was not exactly followed</td>
<td>62</td>
<td>85, 15, -</td>
</tr>
<tr>
<td>Do not report the presence of key missing data that could bias the results</td>
<td>68</td>
<td>76, 23, 1</td>
</tr>
<tr>
<td>Ignore violations of assumptions because results may change to negative</td>
<td>64</td>
<td>71, 28, 1</td>
</tr>
<tr>
<td>Modify a measurement scale to achieve some desired results rather than adhering to the original scale as validated</td>
<td>55</td>
<td>79, 20, 1</td>
</tr>
<tr>
<td>Report power on the basis of a post hoc calculation, but make it seem like an a priori statement</td>
<td>54</td>
<td>76, 23, 2</td>
</tr>
<tr>
<td>Request to not properly adjust for multiple testing when “a priori, originally planned secondary outcomes” are shifted to an “a posteriori primary outcome status”</td>
<td>56</td>
<td>80, 18, 2</td>
</tr>
<tr>
<td>Conduct too many post hoc tests, but purposefully do not adjust α levels to make results look more impressive than they really are</td>
<td>54</td>
<td>60, 36, 4</td>
</tr>
<tr>
<td>Remove categories of a variable to report more favorable results</td>
<td>48</td>
<td>68, 31, 1</td>
</tr>
<tr>
<td>Do not mention interim analyses to avoid “too much testing”</td>
<td>50</td>
<td>81, 18, 1</td>
</tr>
<tr>
<td>Report results before data have been cleaned and validated</td>
<td>48</td>
<td>56, 39, 5</td>
</tr>
<tr>
<td>Do not discuss the duration of follow-up because it was inconsistent</td>
<td>45</td>
<td>84, 15, 1</td>
</tr>
<tr>
<td>Stress only the significant findings, but underreport nonsignificant ones</td>
<td>42</td>
<td>45, 48, 7</td>
</tr>
<tr>
<td>Do not report the model statistics (including effect size in ANOVA or R² in linear regression) because they seemed too small to indicate any meaningful changes</td>
<td>42</td>
<td>76, 23, 1</td>
</tr>
<tr>
<td>Do not show plot because it did not show as strong an effect as you had hoped</td>
<td>33</td>
<td>58, 39, 3</td>
</tr>
</tbody>
</table>

ANOVA = analysis of variance.

* Based on findings from questions 1-18 of the Bioethical Issues in Biostatistical Consulting Questionnaire, which asked biostatisticians “to estimate the number of times—during the past 5 years—that you, personally, have been DIRECTLY asked to do this.” Data are presented in decreasing order by the percentage of respondents with a perceived severity score of 4 or 5.

† Items were defined as “most severe” if respondents ranked the severity as 4 or 5 on a scale of 0-5.
Questionable research practices

Probably most important

To mention a few

- Sloppiness
- Failure to follow protocol
- Over-interpretation of results
- Failure to publish
- Conflicts of interest
- …
The trial/study protocol

Purpose

- Helps to do a study in a uniform and reproducible way
- Operating manual for investigators and other study personnel
  → a good protocol helps and is not a barrier
- Safeguard for study participants
- Defines the boundaries of the project (approval, consent, …)
Extend of problem

Single-center experience

- 2010-2015
- 499 oncology trials (industry and investigator-initiated)
- Deviation reports filed at Institutional Review Board

Table 1: Details of protocol deviations and responsible factors

<table>
<thead>
<tr>
<th>Type of deviation</th>
<th>Number</th>
<th>Institution</th>
<th>Subject</th>
<th>Sponsor</th>
<th>Schedule management</th>
<th>National holiday</th>
<th>Disease condition</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>360 (0)</td>
<td>12 (0)</td>
<td>2 (0)</td>
<td>0</td>
<td>64 (0)</td>
<td>68 (0)</td>
<td>29 (0)</td>
<td>14 (0)</td>
</tr>
<tr>
<td>Examination</td>
<td>466 (30)</td>
<td>28 (0)</td>
<td>1 (0)</td>
<td>0</td>
<td>1 (0)</td>
<td>0</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Vital signs</td>
<td>31 (0)</td>
<td>28 (0)</td>
<td>1 (0)</td>
<td>0</td>
<td>1 (0)</td>
<td>0</td>
<td>1 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Clinical examination</td>
<td>398 (10)</td>
<td>291 (7)</td>
<td>28 (0)</td>
<td>12 (2)</td>
<td>18 (0)</td>
<td>5 (9)</td>
<td>29 (1)</td>
<td>15 (0)</td>
</tr>
<tr>
<td>Management of samples</td>
<td>17 (0)</td>
<td>12 (1)</td>
<td>0</td>
<td>5 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment</td>
<td>275 (72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration criteria</td>
<td>29 (55)</td>
<td>24 (11)</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Overdose</td>
<td>36 (59)</td>
<td>22 (10)</td>
<td>12 (0)</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Undesire</td>
<td>37 (0)</td>
<td>5 (2)</td>
<td>24 (0)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Therapeutic method</td>
<td>123 (44)</td>
<td>55 (9)</td>
<td>19 (0)</td>
<td>2 (0)</td>
<td>4 (0)</td>
<td>1 (9)</td>
<td>13 (1)</td>
<td>29 (0)</td>
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<tr>
<td>Consent violation</td>
<td>39 (12)</td>
<td>14 (2)</td>
<td>4 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15 (0)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Management of investigational products</td>
<td>11 (0)</td>
<td>7 (4)</td>
<td>2 (0)</td>
<td>2 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Others</td>
<td>57 (37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Eligibility criteria</td>
<td>16 (11)</td>
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<tr>
<td>Stratification</td>
<td>4 (3)</td>
<td>3 (1)</td>
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<td>1 (0)</td>
<td>0</td>
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<tr>
<td>Informed consent</td>
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<td>18 (13)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Protection of personal information</td>
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<td>3 (3)</td>
<td>0</td>
<td>1 (1)</td>
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<td>0</td>
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<td>Case report form</td>
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<td>0</td>
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<tr>
<td>Others</td>
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<td>3 (3)</td>
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<td>0</td>
<td>1 (0)</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>967 (129)</td>
<td>520 (70)</td>
<td>93 (10)</td>
<td>28 (14)</td>
<td>88 (1)</td>
<td>74 (0)</td>
<td>95 (19)</td>
<td>69 (3)</td>
</tr>
</tbody>
</table>

The numbers in parentheses denote serious deviations.

Sasada 2017
Table 1  Details of protocol deviations and responsible factors

<table>
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<tbody>
<tr>
<td>Visit</td>
<td>189 (0)</td>
<td>12 (0)</td>
<td>2 (0)</td>
<td>0</td>
<td>64 (0)</td>
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<tr>
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<td>446 (16)</td>
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<td>1 (0)</td>
<td>0</td>
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<td>Vital signs</td>
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<td>Management of samples</td>
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<tr>
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<tr>
<td>Concomitant medication/activity</td>
<td>39 (12)</td>
<td>14 (2)</td>
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<td>Management of investigational products</td>
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<td><strong>Total</strong></td>
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<td>520 (79)</td>
<td>93 (10)</td>
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<td>88 (0)</td>
<td>74 (0)</td>
<td>95 (19)</td>
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The numbers in parentheses denote serious deviations.
Protocol = ethics application?
A common misunderstanding

Q: “Do you already have a study protocol or at least an outline?”
A: “Yes, I am currently working on the ethics application!”
Protocol = ethics application?

A common misunderstanding

− People often talk about the protocol as being “the ethics application”

→ Although the protocol has to be submitted to the ethics committee and despite the fact that study protocols should usually be written using the Swissethics protocol templates, it has nothing to do with the ethics application per se.
Main issue (root cause) in practice
Physician versus investigator (researcher)
Causal factors in general

On different levels

- Individual traits
- Institutional issues
- Structural problems in science itself

Smith R 2016

The answer that researchers love is `pressure to publish', but my preferred answer is `Why wouldn't it happen?' All human activity is associated with misconduct. [...] they [researchers] have fooled themselves that science is a wholly objective enterprise unsullied by the usual human subjectivity and imperfections. It is not. It is a human activity.
A case of fraud

Swazey JP & Scher SR

It is our sense, primarily experiential and impressionistic in nature, that honesty in research work as a fundamental rule is valued more strongly among scientists than among physicians ... Physicians tend to evaluate research in terms of harm or benefit to patients rather than in terms of adherence to the rigorous norms of scientific investigation.

Poisson R

I believed I understood the reasons behind the study rules, and I felt that the rules were meant to be understood as guidelines and not necessarily followed blindly. My sole concern at all times was the health of my patients ... Maintaining the proper balance between good clinical care and rigid research methods is not an easy task.

Cited in George SL 2016
What can we do about these issues?
Prevention

Best evidence

- The evidence base is incomplete
- Many studies with high risk of bias and inadequately reported
- Even randomized designs were difficult to generalize
Culture
The socialization (way of thinking)
Individual versus general (population)
Thank you for your attention!

Sven Trelle, CTU Bern

References

Sources
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- Female ballerina by David Hofmann on Unsplash
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