

Pathways of high quality and productive research in health sciences

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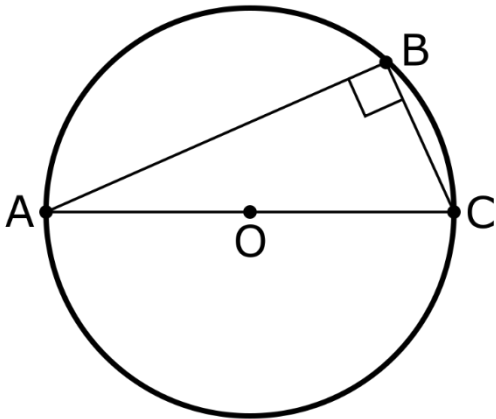
Biomedical Research
Innovation Laboratory

TO ACCELERATE DISCOVERIES

Life expectancy of research results

Mathematics

E.g., Thales's theorem
Thales of Miletus (c. 600 BC)



Principled logic is the most durable method of science

Physics

Newton's law of universal gravitation (1665)



Einstein's theory of gravity, the general theory of relativity (1915)



Health sciences

In 1994, the U.S. FDA (Food and Drug Administration) approved the PSA (prostate specific antigen) test (with 78% FP)



Prostate cancer testing and treatment are unreliable, unsafe, and fail to extend life (2023)

Large and frequent quality deficiencies in biomedical research

Defect	Evidence	Reference
High rate of <u>non-reproducible preclinical research results</u> in studies (75%-89%)	Bayer scientists were able to reproduce only 21% of 67 target-validation projects Amgen scientists found only 11% reproducible in among 53 studies	Prinz, 2011 Begley, 2012
Between 40 to 74% of clinical trials provide <u>uninformative results</u> that are not meaningful for patient care, research or policy-making	The avoidable waste due to inadequate clinical trial methods was estimated at 42% The proportion of clinical trials meeting four conditions for informativeness was only 26.4%	Yordanov, 2015; Hutchinson, 2022
More than half of clinical trials become <u>unfinished or non-reported</u>.	Among completed trials, almost a third not published in the peer-reviewed literature after 4 years. More than half of clinical trials yielding negative results remain unpublished	Ioannidis, 2014, Rees, 2019
Frequent design and conduct <u>deficiencies</u> of preclinical research (22% - 82%)	In study design category, missing power calculation 82.3%) In cell line category, mixed contamination 22.4% In analysis category, the use of chi-square test when expected cells < 5 frequency 15.7% In reporting category, failure to state number of tails 65%	Mansour, 2019

What is NOT a research error?

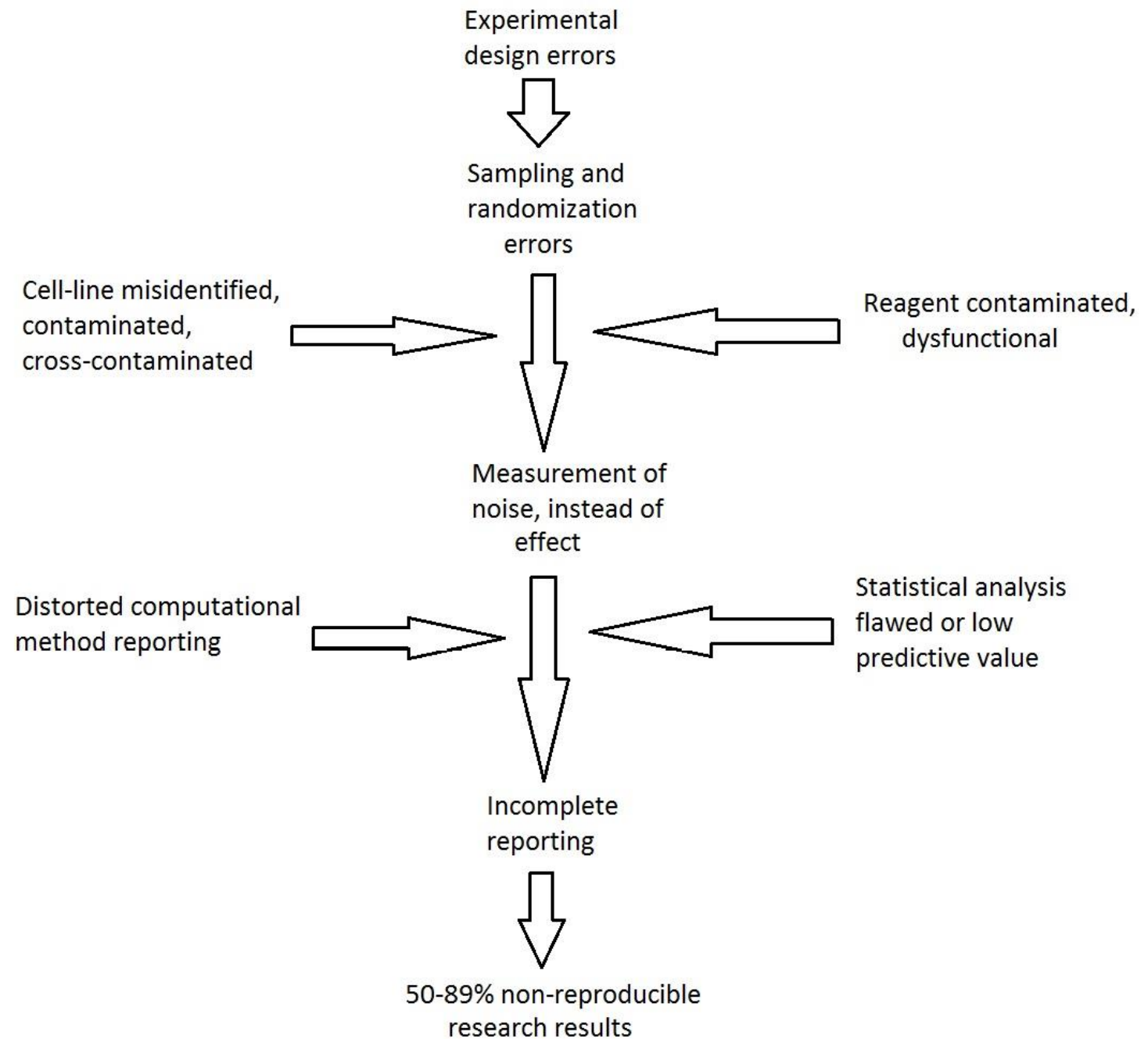
- Statistical tests of the original hypotheses produce many non-significant results
- A clinical trial shows no difference between treatments
- A comparison study shows highly significant differences but the sample size is very small.
- In a series of experiments, there are outlier values without obvious explanation (Spoiler alert: it might lead to Nobel prize winning discovery)
- A researcher chooses an exceedingly ambitious goal that is never achieved.

Reproducibility Deficiencies in Preclinical Research

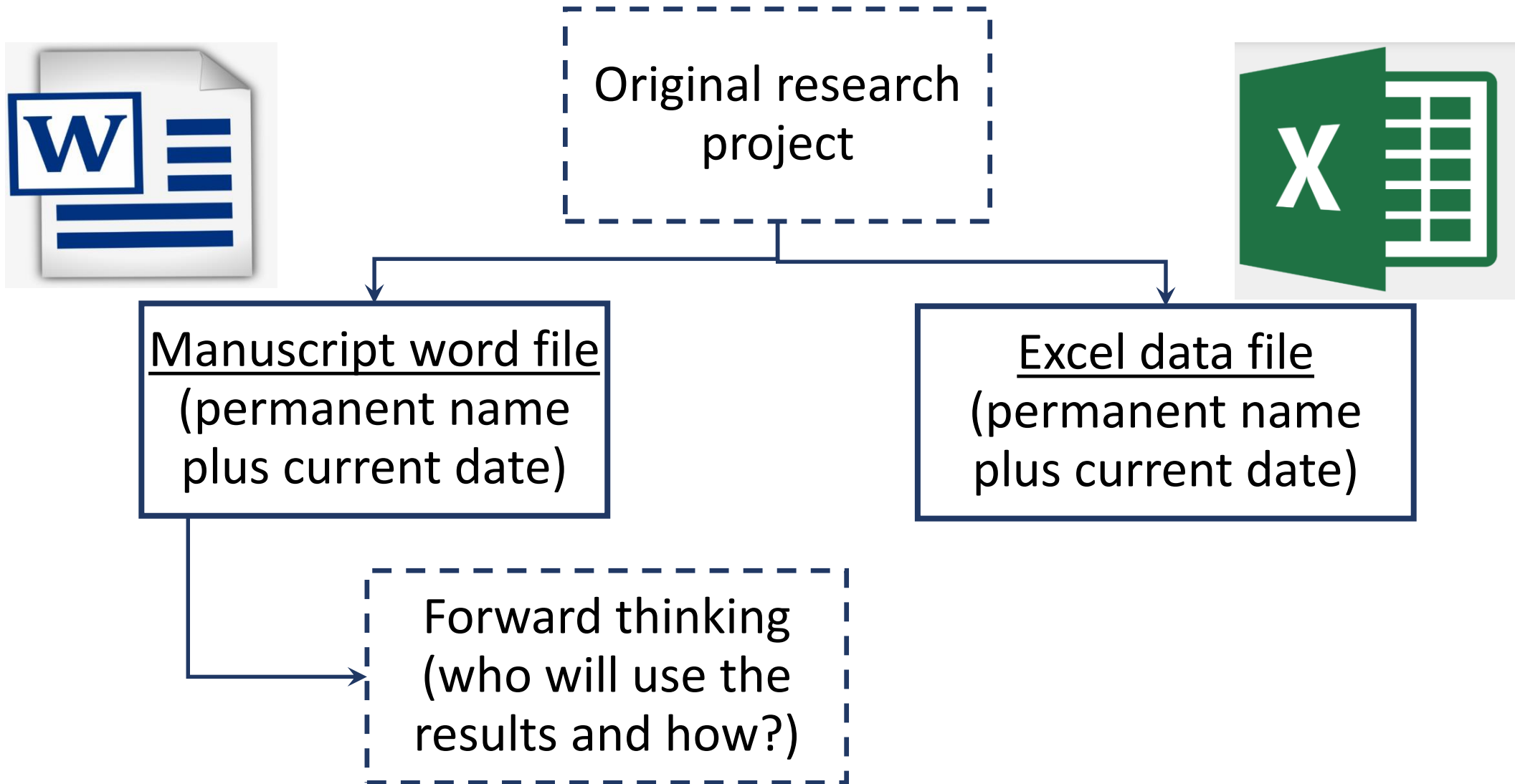
Group	Deficiency	Frequency
Study design	Sample/power calculation error	82%
Study design	Eligibility criteria not mentioned or inappropriate	50%
Study design	Randomization error	29%
Cell lines	Mixed contamination of cell lines	20%
Cell lines	Cell line cross contamination	17%
Cell lines	Misidentified cell lines	14%
Cell lines	Mycoplasma cell line contamination	8%
Cell lines	Cell line bacterial contamination	1%
Statistical analysis	Chi-square used when expected cells frequency < 5	14%
Statistical analysis	Parametric test for nonparametric data	13%
Statistical analysis	Related data independent test & vice versa	12%
Statistical analysis	Mean (SD) used for non-normal or ordinal data	7%

Mansour, N. M., Balas, E. A., Yang, F. M., & Vernon, M. M. (2020). Prevalence and Prevention of Reproducibility Deficiencies in Life Sciences Research: Large-Scale Meta-Analyses. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*, 26, e922016-1.

Sources of non-reproducibility in the research process



FOLLOW VERSION CONTROLLED, FORWARD THINKING RESEARCH PRACTICES!



Data management hygiene

Periodically create successive new versions of the curated dataset with the current date inserted in the filename

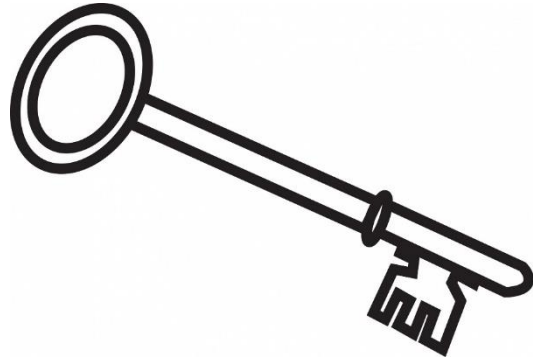
Use clean sheet structure for error prevention and also for publication purposes:

- A. “Read this first” sheet with brief explanation of the variables and data in the workbook
- B. Sheet(s) with the original raw data as they were obtained from an external source
- C. Sheet(s) having the curated sample for analysis but without calculations or transformations
- D. Separate sheet for each table/chart with calculations.

Do not underestimate the power of computers in messing up your data:

Item	Origin	Category		Item	Origin	Category
Orange	California	Fruit		Banana	Brazil	Fruit
Mercedes	Germany	Automobile		Orange	California	Automobile
Banana	Brazil	Fruit		Mercedes	Germany	Fruit
Bentley	UK	Automobile		Ferrari	Italy	Automobile
Grapes	Mexico	Fruit		Grapes	Mexico	Fruit
Ferrari	Italy	Automobile		Bentley	UK	Automobile

The key: Three-point plan for reproducibility



1. Transparency (new NIH requirements)
2. Replication
 - Self-replication
 - Independent replication
3. Triangulation
 - via different experiment
 - via data science comparisons
 - via practical application

Ready to use data for triangulation

Look for confirmatory information in

1. Literature databases (e.g., Cochrane, PubMed)
2. Scientific data repositories (e.g., from Nature Data Repository Guidance)
3. Generalized, experimental data repositories (e.g., UNC Dataverse)
4. Clinical and administrative databases (e.g., Surveillance, Epidemiology, and End Results - SEER)
5. Public health databases (e.g., Behavioral Risk Factor Surveillance System - BRFSS)

Caution: Not everything is accurate or high quality, especially in databases of voluntary contributions



Thank you!

Sept 2013 - EA Balas