Title: Repetition and reproduction of preclinical medical studies: taking a leaf from the plant sciences with consideration of generalised systematic errors.

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Short title: Preclinical medical replicability
Abstract

Reproduction of pre-clinical results has a high failure rate. The fundamental methodology including replication ("protocol") for hypothesis testing/validation to a state allowing inference, varies within medical and plant sciences with little justification. Here, five protocols are distinguished which deal differently with systematic/random errors and vary considerably in result veracity. Aim: to compare prevalence of protocols (defined in text). Medical/plant science articles from 2017/2019 were surveyed: 713 random articles assessed for eligibility for counts: first (with p-values): 1) non-replicated; 2) global; 3) triple-result protocols; second: 4) replication-error protocol; 5) meta-analyses. Inclusion criteria: human/plant/fungal studies with categorical groups. Exclusion criteria: phased clinical trials, pilot studies, cases, reviews, technology, rare subjects, -omic studies. Abbreviated PICOS question: which protocol was evident for a main result with categorically distinct group difference(s) ? Electronic sources: Journal Citation Reports 2017/2019, Google. Triplication prevalence differed dramatically between sciences (both years p<10^-16; cluster-adjusted chi-squared tests): From 320 studies (80/science/year): in 2017, 53 (66%, 95% confidence interval (C.I.) 56%:77%) and in 2019, 48 (60%, C.I. 49%:71%) plant studies had triple-result or triplicated global protocols, compared with, in both years, 4 (5%, C.I. 0.19%:9.8%) medical studies. Plant sciences had a higher prevalence of protocols more likely to counter generalised systematic errors (the most likely cause of false positives) and random error than non-replicated protocols, without suffering from serious flaws found with random-Institutes protocols. It is suggested that a triple-result (organised-reproduction) protocol, with Institute consortia, is likely to solve most problems connected with the replicability crisis.
Key words: False positive; Repeatability; Replicability; Reproducibility; Significance level; Type I error.

INTRODUCTION.

The fundamental methodology by which a hypothesis is tested and validated, including replication model (here referred to as "protocol", see Table 1), to a state at which inductive inference is made from the result, varies, perhaps with little justification, within and between the medical and plant sciences.

Protocols can be identified in the medical sciences (see Methods for more complete definitions): 1) from which inferences are made from non-replicated results ("non-replicated protocols" or 2) which involve reproductions by random institutes followed by meta-analysis ("random-institutes protocols"). In the plant sciences there are protocols in which the entire experiment is repeated three times and 3) the only errors assessed directly are systematic errors among repeats ("replication-error protocols"); or 4) both systematic errors and random errors are considered using a global test, e.g. analysis of variance with "replicate" as one factor to produce one overall result ("global protocols"; individual replicate results not mentioned); or 5) in which three results are obtained ("triple-result protocols", which might also give a global result). There are, of course, other protocols which are not considered here, and those with investigations performed only twice.

There is no sharp distinction between an observational investigation and an experiment ("investigation" used as umbrella term, Table 1; the causation/association interpretation dichotomy does not affect the decision-making discussed in the present article); consider an outdoor experiment with little control over the weather, or a medical intervention in a strictly-
controlled hospital setting. However in general, experiments, which describe most plant science investigations, could be assumed to have MORE control over numerous parameters and confounders, and conclusions from these might have a greater chance of being correct than from “observational investigations”, a term which could be used to describe most medical science investigations. An experiment is designed to reduce background parameter variance so effects of a test group stand out and is also designed to control systematic effects. Therefore, overall, an experimental study on the same theme as an observational study is likely to have less or comparable parameter variance to the observational study and might well also have more control over systematic effects. It is essential that a protocol used for an observational investigation has at least the same or more safeguards against false positives than an experiment.

There is now ample empirical evidence that non-replicated protocols have low veracity. Major studies have tried to reproduce pre-clinical results. From five compilation studies in Freedman et al (1) the maximum percentage of investigations from different disciplines with successful reproduction was 49%. In Begley and Ellis (2) only 11% of "landmark" results from haematology and oncology were reproduced. Amrhein et al. (3) gave an estimate of 47% non-reproducible studies. Similarly, successful reproductions of psychology results were obtained by the Open Science Collaboration (4) at around 35% of studies reproduced. In 2014 Ioannidis famously claimed that an estimated 85% of research resources were wasted (5,6) and in this article we use the (very rough and for illustration only) location estimate of ~80% to represent false positive prevalence (which actually ranges from 47% to 90% depending on the subject) as a percentage of total medical science positive results.

As medical science was judged by researchers in the previous paragraph using reproduction study compilations, it follows that some form of replication is bound to provide one
solution to the medical science crisis. Two questions remain: 1) are there any other solutions? and 2) what rules should replications obey? In this article we explore methodologies found in other sciences and question theoretically whether protocols found would be sufficient to transfer to the medical sciences.

Of considerable importance is that many medical professionals have no experience of first set success followed by failure of a second set, the differences being due to unknown systematic errors or random error. (Future experience experience of replication will likely be self-reinforcing.)

A frequent lack of sufficient consideration of systematic errors, the definition of which follows, appears at first sight to present a problem. We ignore simple definitions such as an offset which is “constant” or “always in one direction”, preferring a working definition in which a systematic error is caused by nuisance parameter(s) which usually give on average an offset to a result (Table 1). (Note that "systematic error" is used in the present article to refer to effects from parameters which can potentially give false positives.) The physicists Norena et al. (7) have given a mathematical definition of systematic error; allow at least some systematic errors to be given a probability density function (pdf); and total systematic error to be calculated by quadratic addition of individual components. They state that nuisance parameters are found by identifying the science "that is invariant under arbitrary rescalings of the nuisance quantities". (From this mathematical definition some nuisance parameters might give overall symmetric effects i.e. only overall affect random error, depending on the definition of the latter.) Many systematic errors have their own random component which does not preclude some having constant values in particular replicates. Even so, theoretically, total systematic differences between replicates could be identified by increasing sample size and observing differences which do not diminish beyond
random error effects. This would not need identification of particular nuisance parameters (although identified confounders could be of considerable importance; "confounder" and "nuisance parameter" are used here synonymously).

In physics some experiments are repeated many times and precise estimates of total systematic error given. In eight of ten examples in Supplemental_file_S1 (the first found by Google Scholar search for "physics" and "systematic error" in October 2021), some of which were highly controlled experiments, systematic error estimates were larger or similar to random error and overall a (rough) median total-error estimate (usually not estimated, here by quadratic addition) was double the random error. It should be noted at this point there is no reason to suppose that medical science investigations would fare any better, and there are some reasons to suppose that observational investigations might fare overall a lot worse than experiments, although such precise systematic error estimates in medical science would never become available.

One assumption could/should be that both random and systematic errors potentially affect all investigations. Supplemental_file_S2 gives 100 examples of triplicated plant science studies from the 1980s and 1990s (these are not part of the surveys and were found by searching plant science journals for the text "three"). Ten of the examples given are described here as presenting "replication-error protocols". It is quite striking that these protocols involve direct assessment only of systematic errors (standard errors/deviations given among replicates without further assessment), in direct contrast to many medical studies which only assess random error. If numbers of individuals (N) are large (reducing random error) then the replication errors represent systematic differences between the replicates which will not change significantly as N is increased further. The implicit assumption being made is that there is ALWAYS systematic error
and the results presented in each article indicate that these probably do not disturb group mean/median differences. Presumably these research groups regarded systematic errors as potentially of greater importance than random error (and indirect estimation is given later to indicate this relative importance might also often apply to the medical sciences).

It is critical to realise that repetition (see Table 1 for "repetition", "reproduction" and "replication") is not simply continuing to gather the same data (which might result in apparent ~5% error rate due to random error alone, ignoring the fact that a systematic error might affect the whole dataset), but that as many possible sources of systematic error are reset between repeats as advisable, these decisions being difficult and subject-dependent.

The "growth cabinet dilemma" illustrates the difficulties involved. For a hypothesis that a drug has an effect, imagine restricted resources with growth cabinets available with necessarily non-random plant placement and some bias e.g. drug to be sprayed from one side. If a positive result is obtained and a repeat planned, should the repeat be performed in a second cabinet (with identical specifications) available, or in the first cabinet again? Either way there is risk and asymmetry between positive and negative results (assume no unknown systematic differences other than via cabinets).

If the first cabinet is used again with:

(a) a negative result: results differ due to random error; most likely the hypothesis is false (proportion of false to true negatives always assumed negligible for an adequately powered study);

(b) a positive result: the result might only be obtainable in that cabinet. Either 1) the hypothesis is true: the drug had effect; or 2) the hypothesis is false: some quirk unconnected with the drug, which might apply only to this cabinet, gave the result, or 3) the hypothesis with the expected
domain (here all growth cabinets) is false but a hypothesis with a more restricted domain is true
e.g. the drug has effect only under those conditions in the first cabinet (remembering that "hypothesis testing" is really "hypothesis plus method testing").

If the second cabinet is used with

(c) a negative result: results differed due to random error or minor (unmeasured i.e. unknown confounder) differences between cabinets; 1) hypothesis is most likely false, but 2) a hypothesis with a more restricted domain might be true (i.e. drug might have effect in conditions given by the first cabinet but not the second).

(d) a positive result: hypothesis is most likely true and minor (unmeasured i.e. unknown confounder) differences between the cabinets did not affect the result. A more restricted hypothesis is not necessary and the chances that a quirk unconnected with the drug has given the result is less.

The dilemma comes from the fact that (b) is more likely than (d), but (d) is more desirable than (b).

Here the scientist will probably choose the second growth cabinet i.e. will reset unknown cabinet systematic effects, allowing induction (to all cabinets of that specification) from a repeated positive result. Now if we replace the second cabinet with one with known systematic differences the dilemma still applies and the decision is more difficult. In this case the plant scientist might choose the first cabinet again, on the basis that it might be better to have two positive results with the possibility that a hypothesis with a more restricted domain is true (to be determined later) than to risk changing the conditions, or might choose the second cabinet, on the basis that it is better to have a more generalisable conclusion with the possibility of later back-tracking with a subsequent repeat if necessary in the first cabinet (this is a possible argument in
favour of consecutive, rather than parallel, repetition). (Of course, with unlimited resources the experiment could be done three times in one cabinet; three times in cabinets with identical specifications; and three times in growth cabinets with different specifications - but in the real world there are always limited resources.)

Obviously the above dilemma can be translated to the medical sciences by replacing plants with humans and cabinets with clinics.

As it is always the case that repetition involves some resetting of systematic error values (from unknown confounders or slight differences in known confounders; either inadvertently or through design; note in the above example we haven't considered confounders due to timing) it follows there is no fundamental distinction between a repetition and a reproduction (even though these terms might be useful, see Table 1), only one of degree; the latter having more possibilities for, and probably greater effects from, sources of systematic error. Note also, for a large non-replicated dataset with systematic-error values probably reset within it, non-random dataset division of the dataset is a form of repetition and the same rules apply. Although non-random division might seem artificial, especially if patients have been obtained in a continuous stream, even so batching is equivalent to repetition.

Now consider the "random-institutes protocol", in which a non-replicated result is published, followed by reproductions by random Institutes throughout the world, followed by meta-analysis. At first sight this seems reasonable until the following is considered:

1) In the Introductions/Discussions of articles, some medical scientists continue to make inferences from other (different) non-replicated studies; formulation of a further hypothesis often follows a line of reasoning with a network of interconnected strings of hypotheses and every false link in this network increases the chances of a false formulated hypothesis. (It is therefore
possible that the situation regarding false-positives might be self-perpetuating or even get worse. It follows that rules could/should be created so that all inferences are made either from triads of reproduced results (all giving the same results; with no contradictory evidence), or meta-analyses or, with new protocols, inferences from higher-level evidence which might become available.

2) The random-Institutes protocol demands that the medical theoretical landscape is flooded with potential nonsense (at a prevalence of ~80%); this is almost certainly the most important criticism because it affects further hypothesis generation; false-positive publications are difficult to counteract and cause immediate damage in the theoretical arena; a non-effectively-countered false positive will influence the entire scientific period before effective counter (see Table 1), including hypothesis building, experimental design, conclusions made, directions taken towards patient cures; possibly with disastrous effect.

3) the numbers of patients involved per hypothesis is sometimes very large and, relative to another protocol, might be unethical.

4) it is never known just how many Institutes will reproduce the study, and many might not publish a negative result, giving a rather dubious basis for a meta-analysis. (Note it is not possible to build a network of ideas or an association network of parameters from negative results and therefore in many cases these are of secondary importance to theoreticians.)

5) The responsibility for showing whether a hypothesis is true or not does not rest with the original researcher.

One example of a random-Institutes protocol is provided by the analysis of the statin-associated ABCB1:c.3435T>C (formerly MDR-1:c.3435T>C) single nucleotide polymorphism (SNP). An early paper in 2010 suggested this polymorphism influenced dose decrease or
switching between simvastatin and atorvastatin therapy (8). Subsequently at least 116 papers were published - at a time when it was not yet known whether the SNP actually has an effect or not! i.e. point 2): the theoretical landscape was potentially flooded with false positives. Note that this criticism alone is enough to apply for change in protocol and the way in which Introductions/Discussions are written (see above). At least 86 investigations were performed with patients (i.e. point 3) and it is not known how many studies were conducted, only published, before a meta-analysis was performed (point 4) (9,10).

From the fact that the level of evidence differs considerably (see Discussion) among the five protocols given above, it is of some interest to know protocol prevalence in the two sciences.

The aim of the present study was therefore to assess prevalence of four of the five protocols mentioned above in the medical and plant sciences. (As a non-replicated study can contribute to either a non-replicated protocol or to the random-Institutes protocol, prevalence is only given for the former and meta-analysis prevalence is only given for reference.) The hypothesis was that there were differences in protocol prevalence between the two sciences. The study was repeated twice with surveys of articles from 2017 and 2019 and results were also distributed according to Journal impact factor. The survey question followed PICOS guidelines: from a study selected from the comparative fields of medical and plant sciences, which of the protocols (defined above) were used for a main result concerning differences between categorically distinct groups? (Exclusion and inclusion criteria for study designs are given in the methods.)
| Term. | Usage in the present article. |
|-------|-------------------------------|
| "Protocol" | The fundamental methodology by which a hypothesis is tested and validated, including replication model, to a state at which inductive inference is made from the result. |
| "Study set" | Replicate = independent batch of subjects/plants and analysis. |
| "Subject" | Patient, human subject, plant or other organism (non-interacting<sup>a</sup>). |
| "False positive" | Incorrect assignment of a positive result (possibly Type I, due to random and/or systematic error). |
| “Investigation” | Umbrella term including experiments and observational investigations. |
| "Replication"<sup>b</sup> | Umbrella term including repetition, reproduction, and other types. Gómez et al. has 18 classifications; 10 fields; 79 overlapping types. |
| "Repetition"<sup>b</sup> | A repeat is a study using a new subject group, i.e. biological repetition, perhaps at another time, by the same researcher/apparatus/site<sup>c</sup> using the same protocol<sup>c</sup> following the resetting of some possible sources of systematic errors. From literature: "Internal replication" (11) or "Literal replication" (12). |
| "Reproduction"<sup>b</sup> | Study by other researchers following the same protocol<sup>c</sup> (automatically resetting some or many sources of systematic error). From literature: "External replication" (11) or "Operations" replication" (12). Precisely; modifying elements from Gomez et al. (11): mostly site/researcher/apparatus<sup>d</sup> replications i.e. different sites/researchers/apparatus. Sometimes are also /population replications i.e. different populations. |
| "Partial result" | Non-replicated result. |
| "Full result" | Triplicated result. |
| "Counter" | To counter an error means that a previously obtained partial positive result has a chance that it would not be replicated, which would indicate it is probably false. |
| "Systematic error" | Source(s) of systematic error are recognised when an average offset to a main result appears from a particular replicate (with sufficient values to depress random error effects), or where a nuisance parameter consistently gives a (varying) offset as it is varied. A source might include known, unknown and/or combinations of nuisance parameters. A systematic error is the offset given by such a replicate, or nuisance parameter(s), to a result or individual datapoint. |

NOTE: <sup>a</sup>This article is concerned with investigations with non-interacting subjects or where parameters of interest are not affected by inter-subject interactions.

<sup>b</sup>All replication terms include first study set in count e.g. three repeats means three instances.
Numbers of subjects allowed to vary (sacrificing precision in the weighting of some systematic error values). Parameters might have systematic differences between replicates; these might be averaged. If a result is declared then systematic differences and/or random error are indicated not to have unduly disturbed the result.

d If organizational bodies provided defined lists of elements (e.g. "site", "researcher", "apparatus", "population") of study structure then every study could use succinctly defined types of replication.
Results

Survey results. The numbers of articles with triplication protocols (global and triple-result protocols pooled together) differed significantly between the sciences in both 2017 and 2019 with very low p-values (p<10^{-16}) by cluster-adjusted chi-squared tests, with far more found in the plant sciences, 53 from 80 (2017: proportion 66%, 95% binomial confidence interval (C.I.) 56%:77%) and 48 from 80 (2019; proportion 60%, C.I. 49%:71%) than in the medical sciences: 4 from 80 in both years (proportions 5%, C.I. 0.19%:9.8%) (Supplemental_file_S11). (The distributions of protocols also differed significantly in both years by Fisher's exact tests, not accounting for clustering, and effect sizes are given in Supplemental_file_S11).

The prevalence of the different protocols appeared to be reasonably constant across impact factors (Tables 2 and 3) but trends were not analysed statistically and, additionally, differences between 2017 and 2019 were also not analysed statistically (most notably a large apparent difference between the triple-result and triplicated global protocols between 2017 and 2019).
Table 2. Prevalence of various protocols (defined in Methods), estimated from a survey of 160 plant and medical science articles published in 2017.

| Impact factor: | $1 < 2$ (n=20) | $2 < 3$ (n=20) | $3 < 4$ (n=20) | $>4$ (n=20) | All (%) (n=80) |
|---------------|----------------|----------------|----------------|------------|--------------|
| Protocols in plant sciences. | | | | | |
| Triple result, | 2 | 2 | 1 | 2 | 7 |
| Triplicated study, global result | 11 | 7 | 9 | 13 | 40 |
| Double result | 2 | 3 | 3 | 3 | 11 |
| Duplicated study, global result | 4 | 2 | 0 | 0 | 6 |
| Non-repeated study | 1 | 6 | 7 | 2 | 16 |
| **Total** | **20** | **20** | **20** | **20** | **80** |
| Triple or triplicated global | 13 | 9 | 10 | 15 | 47a |
| Replication-errorb | 0 | 1 | 2 | 5 | 12 |
| Meta-analysis | 0 | 0 | 1 | 1 | 2 |
| Protocols in medical science. | | | | | |
| Triple result, | 0 | 0 | 1 | 0 | 1 |
| Triplicated study, global result | 0 | 0 | 0 | 3 | 3 |
| Double result | 0 | 0 | 0 | 1 | 1 |
| Duplicated study, global result | 0 | 0 | 0 | 0 | 0 |
| Non-repeated study | 20 | 20 | 19 | 16 | 75 |
| **Total** | **20** | **20** | **20** | **20** | **80** |
| Triple or triplicated global | 0 | 0 | 1 | 3 | 4a |
| Replication-error | 0 | 0 | 0 | 0 | 0 |
| Meta-analysis | 2 | 1 | 2 | 1 | 6 |

NOTE: See Supplemental_Tables_S3:S6 for articles.

a indicates proportions significantly different by Chi-squared tests with adjustments for clustering. bReplication errors in articles were either given as standard errors or standard deviations among replicates.
Table 3. Prevalence of various protocols (defined in Methods), estimated from a survey of 160 plant and medical science articles published in 2019.

| Impact factor: | 1 < 2 (n=20) | 2 < 3 (n=20) | 3 < 4 (n=20) | ≥4 (n=20) | All (%) (n=80) |
|---------------|-------------|-------------|-------------|----------|--------------|
| Protocols in plant sciences. |             |             |             |          |              |
| Triple result, | 3           | 7           | 8           | 11       | 29           |
| Triplicated study, global result | 4           | 6           | 7           | 2        | 19           |
| Double result | 3           | 0           | 2           | 1        | 6            |
| Duplicated study, global result | 0           | 0           | 0           | 0        | 0            |
| Non-repeated study | 10         | 7           | 3           | 6        | 26           |
| **Total** | **20** | **20** | **20** | **20** | **80** |
| Triple or triplicated global | 7           | 13          | 15          | 13       | 48<sup>a</sup> |
| Replication-error<sup>b</sup> | 2           | 0           | 0           | 1        | 5            |
| Meta-analysis | 0           | 0           | 0           | 1        | 1            |
| Protocols in medical science. |             |             |             |          |              |
| Triple result, | 0           | 0           | 1           | 1        | 2            |
| Triplicated study, global result | 0           | 1           | 1           | 0        | 2            |
| Double result | 0           | 0           | 0           | 1        | 1            |
| Duplicated study, global result | 0           | 0           | 0           | 0        | 0            |
| Non-repeated study | 20         | 19          | 18          | 18       | 75           |
| **Total** | **20** | **20** | **20** | **20** | **80** |
| Triple or triplicated global | 0           | 1           | 2           | 1        | 4<sup>a</sup> |
| Replication-error | 0           | 0           | 0           | 0        | 0            |
| Meta-analysis | 2           | 0           | 2           | 1        | 5            |

NOTE: See Supplemental_Tables_S3:S6 for articles.

<sup>a</sup> indicates proportions significantly different by Chi-squared tests with adjustments for clustering. <sup>b</sup>Replication errors in articles were either given as standard errors or standard deviations among replicates.
DISCUSSION.

It is clear from the results that all five protocols mentioned in the Introduction were still active in 2019, and that protocols involving triplication had much higher prevalence in the plant sciences, as assessed by cluster-adjusted chi-squared tests. (Conclusions from Fisher tests should be made with caution as these were not adjusted for clustering.)

Possible trends across years or impact factors were not tested statistically on the basis that more data would probably need to be collected for successful analysis. The most important aspect is that the main result has been repeated, not that this was performed in different years, which is merely coincidental with the time taken for completion of a study part and constitutes a nuisance parameter which gives a systematic error value which was reset (probably along with many other systematic error values which were reset despite the defined protocol). The fact that this type of reasoning applies to ALL repeated investigations is a major point being made in this article. Two positive results were obtained (three would be better) showing that any nuisance parameters reset did not disturb the main conclusion, which is that there were more triple-result plus triplicated-global result protocols performed in the plant sciences than in the medical sciences.

Note that this does not show that final conclusions from results in the plant sciences were any better than the medical sciences, because the random-Institutes protocol demands that all non-replicated results be published and the utilisation of meta-analyses (for inference) has not been assessed (only the prevalence of meta-analyses is given). However, it does show that inferences made from the plant sciences overall are likely to be considerably more effective than inferences made from non-replicated protocols, for reasons discussed below especially with regard to the triple-result protocol. As no equivalent of Friedman et al. was found for the plant
sciences i.e. empirical evidence is lacking to prove this point, the arguments, although strong, remain theoretical. Problems with the (weaker) global protocols are not considered in depth in this article.

As the plant science community has not abandoned the triple-result protocol after at least 150 years of usage, despite the pressures from costs, time and other resources, it can be assumed, following the regrettable lack of archiving of all results (especially those in which a first set gave a positive result but a subsequent set indicated a false positive) that often triplication is regarded as necessary in order to ensure acceptably low numbers of false positives. In any case, the present calamitous situation in medical science indicates that the burden of proof should lie in the direction to prove that triplication is not necessary, rather than vice versa. In other words, any proposed protocol should be directly comparable with present protocols involving triplication.

The reason why triplication (used in several protocols) gives the standard minimum number of replicates for a quantitative result is that SOME components of systematic errors e.g. some systematic errors which give a constant value to one replicate and then another value to the next replicate, will only be combined with maximal efficiency, of reduction in confidence interval, by triplication. It is also rather doubtful whether some aspects of statistical tests work efficiently, e.g. with a global protocol, with less than three points. Compare the $t$ distribution with individuals: the 95% confidence interval is non-defined with one individual; 12.7 with two individuals, 4.6 with three individuals and 3.2 with four individuals; the point being that 12.7/4.6 is much larger than 4.6/3.2 and subsequent ratios and therefore three replicates are maximally efficient in terms of reduction in confidence interval (and similar arguments can be extended to some systematic error values) (13).
One (extreme, but correct) protocol which corresponds to repetition, would be to non-randomly divide a dataset into three parts: if a partial result (see Table 1) is then obtained three times then systematic differences between the three parts have not disturbed the result (and this also effectively eliminates consequences due to random error); this is a type of repetition. However, whether reviewers would accept this depends on which systematic errors they think should be reset, and which should not be reset (i.e. which confounders between replicates are not allowed, and which should be reset). These decisions are difficult and subject-dependent (see the growth-cabinet dilemma in the Introduction). A researcher could argue, correctly, that this starts off with consistently obtainable partial positive results and then future subsequent replications would allow possible expansion of the systematic domain under which consistent partial positive results are obtainable. However, a subsequent negative reproduction would likely mean that the hypothesis is false or that the systematic domain has not been adequately described in the methods. The dilemma is therefore whether to try to expand the systematic domain to start with, or whether to be content at the beginning with consistently obtainable partial positive results with a restricted domain (with the risk of a false positive i.e. a result not connected with the hypothesis). In either case, the end goal (see below) MUST be to obtain consistent partial positive results by reproduction.

The lack of ability for most investigations to determine effects from systematic errors can be illustrated by considering genetic background as one possible source of systematic error. If a partial result is supposedly obtainable in one genetic background, then it needs to be shown that this result can be consistently found in one genetic background, and not in others. A reproduction can be asked for in the same genetic background. If it is not positive the most likely explanation is that the main effect hypothesis is false. Likewise, if only two partial results have been
obtained, and these in different genetic backgrounds with different results (positive and negative), the conclusion is still that the main effect hypothesis is most likely false and that genetic background is only one of many (probably hundreds of combinations of) possible systematic errors. To actually show that genetic background is the cause of differing results, as opposed to other biological or non-biological systematic differences, would require a considerable number of reproductions giving consistently different results in several different genetic backgrounds, and a very large study in which many other possible sources of systematic error have been reset and therefore eliminated from discussion i.e. most investigations are NOT designed to indicate actual sources of systematic error, including genetic background.

The definition of systematic errors in the Introduction is already fairly general, but (the false-positive-liable subset of) systematic errors can be generalised further to define “generalised systematic errors” to include all types of error and events which can cause false positives, apart from random error. This has several ramifications:

1) These now include effects from the following components: (a) events such as human blunders, as well as administrative and technical errors; (b) unknown confounders: search for new knowledge demands acknowledgement these might exist; (c) known confounders which have been inadequately adjusted for (linear adjustment is sometimes used necessarily without justification); (d) combinations of components (a) to (c).

2) All components have associated risks and can potentially be countered by replication (whereas many components CANNOT be countered by adjustments or exclusion); indeed this gives the reason why replication is irreplaceable for the testing of any scientific hypothesis concerning categorical groups to which frequentist statistics can be applied (remembering that if systematic errors are reset within a large non-replicated dataset, then non-random division of the dataset is a
type of repetition). Lack of replication might not be the only problem besetting medical science, with a possible list including lack of randomization, blinding, sample size calculation, inclusion and exclusion criteria pre-specified, statistical analysis plan pre-specified, etc. often given [Benjamin et al.]. However, reproduction might well counter some or all of these problems if the other Institutes do not fall into the same traps.

3) The sets of "generalised systematic errors" and "systematic errors", as defined, at first sight might seem to differ to a large extent but this is not correct. In fact the (false-positive-liable subsets of the) sets are almost identical because almost all components, including many human blunders, which give false positives will do so via offsets i.e. systematic error. In contrast, for example, components which give missing data are likely to give negative results. Components which are added to systematic errors to give generalised systematic errors might come from obscure effects e.g. from human blunders where somehow missing data gives a false positive without offsets. There is no general prescription by which both sets can be a priori delineated and both are subject-dependent.

4) A very rough estimate of generalised systematic error prevalence can be obtained: it is simply ~80% (see Introduction) minus ~5% random errors i.e. it can now be said that (very roughly) ~75% of positive results can be false positives due to generalised systematic errors. This illustrates, together with the examples given in the Introduction, that in all three sciences systematic errors or generalised systematic errors are likely to have a higher prevalence and effect than random error, or at least are already regarded as of considerable concern by many research groups.
As far as random error (which is likely to give the least numbers of false positives relative to other sources of error) is concerned, a triple-result protocol has a large effect on the overall significance level for an investigation.

Triplication has a long history in the plant sciences with examples from the 1890s (e.g. see Escombe (14), p. 587; triplication was recorded from Peter (15)). In 1919, Fisher entered the plant sciences at Rothamsted Experimental Station and when he published his opus magnum in 1925 (16) he almost certainly would have expected that optimal science would be performed with a triple-result protocol i.e. using a significance level of $p < 0.05$ three times. It is clear from his 1929 paper he regarded replication as more important than the $p < 0.05$ rule (see Fisher (17) and later editions of (16)) and there are plenty of early examples of triple-result protocols (e.g. Table II in Preston (18): three sets of measurements gave $p < 0.05$; Table 6 in Lamm (19): three plant population samples gave $p < 0.05$; Table 4 in Thomas and Hill (20)).

While combining $p$-values is controversial, two techniques ($0.05^3$ and Fisher's method: chi-squared from $-(2 \times 3 \times \log_e(0.05))$, 2 degrees of freedom) give a non-replicated equivalent of $p < 1.25 \times 10^{-4}$ (Lyons (21,22)), although a more accurate equivalent is likely to be lower than this even only considering random error (see Vovk and Wang (23)). If the value is meant to represent total error then systematic errors will make an alpha control equivalent (covering different investigations) even lower. It follows that a large dataset which is to be non-randomly divided cannot give a full result (see Table 1) if the overall $p$-value is higher than $10^{-4}$. It is sometimes argued that different sciences use different significance levels, but this does not mean that there isn't a minimum requirement which, if breached, is unacceptable, and the original minimum requirement was $p < 0.05$ three times. (Separately, for genome-wide association studies, $p < 5 \times 10^{-8}$ is equivalent to $p < 0.05$ after adjusting for numbers of human tagging SNPs.
(24,25); lack of clarity concerning multiple-correction boundaries is an additional minor reason for replication.)

Other discussions of p-values from which it could be concluded that $p < 0.05$ alone is unacceptable are given by Benjamin et al. (26) and Randall and Welser (27). Benjamin et al. (26) suggested lowering the significance level to 0·005 for a non-repeated investigation and Randall and Welser (27), in a replication network publication (https://replicationnetwork.com), state that "$p < 0.01$ should be the loosest recognised standard of statistical significance, not the most rigorous". To provide bases for inference both of these, alone, would be particularly weak compared with the protocols suggested below, mainly because of lack of counter of generalised systematic errors but also because for random error these are weaker than triplication of a result at $p < 0.05$. One reason for Amrhein et al.'s (3) attack on p-values is that $p < 0.05$ is expedient and it is true that p-values might not provide the only hurdle necessary to justify even a triplicated result, see Lyons (21). However there seems no reason why p-values should not also be reported to one significant figure, if only for meta-data purposes, especially as significance levels are disputed and many effect sizes confound p-values with absolute effect sizes (Vargha and Delaney's A statistic being an exception) and do not make p-values redundant. (Note also there are substantial asymmetries between evidential requirements for positive and negative results, with negative result validity relative to power and standardised effect size, whereas with positive replicated results these parameters only play a supportive or tangential role and detailed considerations are not given in the present article.)

Perhaps most importantly, all discussions on p-values, while important, might tend to distract from more important problems facing investigations concerning generalised systematic errors.
Despite considerations from all of the above, reasons might be given for NOT replicating a result (or non-random division of a dataset) which broadly fall into the following categories: (i) It might not matter if non-true (meaning not inductive to a general population) results are published, as long as true results are also published. (ii) There must be another approach by which more veracity can be extracted from the results obtained at present. (iii) Medical investigations are costly. (iv) Ethics requires minimal numbers of patients to provide results. (v) The random-Institutes protocol is sufficient and if all results were published, this would also be efficient. (vi) Hypotheses with narrow domains would counter most false-positives.

Some answers are already given. (i) This is the most challenging, as this depends on the clarity of the theoretical arena used by theoreticians to formulate new hypotheses, which is difficult to quantify. This is discussed with random-Institutes protocols in the Introduction. (ii) No approach (other than replication) which tries to adjust for, or otherwise counter, confounders can deal with all the components of generalised systematic errors (see above). (iii) Investigations are costly in all sciences. However, it is true that different protocols could be compared using a health-economic analysis with reproducibility as a desired outcome. (iv) The random-Institutes protocol is likely to involve far more patients than suggested protocols (given at the end of the Discussion) which are therefore more ethical. Even in the minimal case the numbers of patients involved in trying to show that a result is reproducible are likely to be the same or similar. The non-replicated protocol should be discounted as unethical because of the considerable patient suffering that will continue following false-positive publications, which have high prevalence. (v) Arguments against random-Institutes protocols have already been discussed. It is doubtful whether publication of all results could be achieved with the present (justifiable) pressures for positive-result publication. Partial results and failed investigations could/should be archived for
meta-data purposes. Even though an important consideration is at what point a result is allowed to enter theoretical discussion, the main concern of the present article is not really publication but establishment of truth or falsehood of a hypothesis. (vi) Hypotheses with narrow domains reduce p fishing but do not counter false positives due to generalised systematic errors.

The triple-result protocols found in the plant sciences have only one form, namely from repeats, rather than reproductions. To illustrate the difference, generalised systematic errors (for a particular investigation) can be divided into those potentially countered by repetition and reproduction ("batch errors") and those potentially countered only by reproduction ("persistent errors"). It can now be said that the triple-result (repeat) protocols found in the plant sciences effectively counter batch errors and random error but not persistent errors. This is an important admission, because it is quite possible that the numbers of types of, and prevalence of, persistent errors are greater overall for observational studies than experiments. (Unfortunately relative prevalence of batch and persistent errors are unknown in any science due to insufficient archiving of failed investigations.) This is also likely to be the original reason why non-repeated research was and is published in the medical sciences i.e. that the prevalence of persistent errors was/is too high to recommend repetition because repetition would result in many triplicated false-positive results. It therefore might have been thought better to publish and let someone else (who is likely to reset persistent errors) confirm the result. The flaws in this argument are that even with one partial result the hypothesis is most likely false (Friedman et al. (1)), but a subsequent partial negative is likely to be blamed on systematic differences e.g. genetic background, rather than acknowledge a true negative, and feeding into a random-Institutes protocol has the flaws mentioned earlier. The point is that methods must be developed which allow consistent partial positive reproductions in order to determine a full positive result.
If a partial positive result does not repeat positively, there is no full positive result and the hypothesis is most likely false. If it does not reproduce positively, there is no confirmed full positive result and the default is still that the hypothesis is false i.e. a partial result does NOT show that a hypothesis is true, not even with a restricted domain.

If positive results are obtained several times by repetition but a reproduction is negative, the most likely explanation is still that the hypothesis is false, although there is a slight chance that the hypothesis could be true with a restricted domain.

It follows from the considerations of batch and persistent errors that in the medical sciences it would be unwise to adopt the triple-result (repeat) protocols used extensively in the plant sciences, because huge numbers of triplicated false-positive results might be produced. A stronger protocol should be considered with mixtures of repetitions and organised reproductions, as such protocols are likely to have stronger safe-guards against false positives. This could be achieved in several ways.

In one efficient protocol a researcher might repeat a result and then ask another Institute to reproduce the result: note that decisions concerning information flow between Institutes would be difficult and subject-dependent. If the repetition is positive and the reproduction is negative it is not possible to say whether the hypothesis is true or false (negative being the default position) because of potential persistent errors. Probably the research would finish at this stage because it would be recognised that either the hypothesis or methods need changing. However, by feedback the researcher could re-assess the situation, redefine the domain under which a positive result is supposedly obtainable (or repeat the result with an optimised domain/procedure), and then ask for further reproduction. This feedback process could be continued until the original researcher can define the methods/domain which allow partial positive reproduced results to be obtainable.
consistently, and only then would a confirmed full positive result be declared. In other words the onus would be on the original researcher to define the methods and domain under which consistent organised-reproduction partial positives can be obtained. A confirmed full positive result would only be declared with three organised reproduction partial positives.

Replication decisions concerning which systematic errors are to be reset or not, as well as which information should transfer between cooperating Institutes, are difficult and subject-dependent. A possible model for the latter might resemble that used in the discovery of the Higgs boson in which a consortium of two Institutes, the ATLAS and CMS, cooperated by allowing only top personnel to communicate between Institutes (21) (note that these Institutes were looking for a p-value below five sigma i.e. $3 \times 10^{-7}$, twice).

The triple-result (organised reproduction) protocol would effectively counter, in order with the most important first: 1) batch errors, 2) persistent errors and 3) random error with a nominal equivalent of $p < 10^{-4}$. Decisions concerning inter-Institute information flow would be critical. It could also be noted that, in the future, obtaining empirical evidence that this actually works will be considerably easier to obtain than for random-Institutes protocols. Additionally, it could be argued (rather weakly) that this protocol should take place after publication of a pilot study (here non-replicated studies are regarded as pilot studies).

Lastly, if a discipline wishes to pursue a weaker protocol, then first they have the responsibility to produce evidence that this can be used in practice.

In answer to the two questions posed in the Introduction: 1) if the rationale concerning generalised systematic errors is correct then there is no solution to the medical science crisis which does not involve replication; and 2) organised reproductions with consortia (with feedback to repetition) provide a way to counter persistent errors while avoiding the serious flaws of
random-Institutes protocols. For a quantitative result a triple-result (organised-reproduction) protocol might provide the most effective way to counter systematic and random errors and give the most efficient reduction in confidence intervals in the presence of some types of systematic errors. Overall, a reduction in false-positive publications will be essential to give medical professionals the clarity for correct hypothesis and conclusion generation to provide faster routes towards patient cures.

**Limitations.**

(a) The number of articles assessed was small and the comparison was only made twice (although note the significance level was set at $p = 0.01$, twice, for the same (weak) reasons that the significance level was lowered in Lyons et al. (21) in order to further counter some types of systematic errors for a duplicated result).

(b) Trends over time or impact factor were not tested statistically as more data need to be collected.

(c) There are almost certainly other protocols which have not been considered, although all papers assessed were categorised according to those analysed.

**Conclusions.**

1) The plant sciences have a higher prevalence of protocols which are more likely to successfully counter generalised systematic errors (defined: the most likely cause of false positives) and random error than non-replicated protocols, without suffering from the serious flaws found with random-Institutes protocols.

2) Whichever protocol is adopted (including if a random-Institutes protocol is maintained), no inference should be allowed in Introductions/Discussions of articles from other (different) non-replicated results.
3) A stronger protocol for the medical sciences (without the major flaws found with the random-Institutes protocol) could involve organised reproductions with consortia of cooperating Institutes i.e. a triple-result (organised-reproduction) protocol. A full positive result would only be declared with a partial result obtained three times. This protocol would be notably stronger than that used in the plant sciences, and could be a standard minimum for observational investigations.

**Materials & Methods**

**A) Survey.** Articles \((n = 713, \text{see the PRISMA flow diagram in Fig 1})\) were selected randomly from plant science and medical science journals which were evenly spaced according to impact factor (see below) and were assessed for eligibility for protocol prevalence counts. The first count included papers with p-values for: 1) Non-replicated science (assumed to either contribute to a non-replicated protocol, or to a random-Institutes protocol: not distinguished here); 2) a global protocol (either from triplicated or duplicated studies); or 3) a triple-result or double-result protocol. A second count surveyed papers excluded from the first count to replace first count papers if the following were found: 4) a replication-error protocol or 5) a meta-analysis. All protocols are defined below. Of particular interest was a triple-result protocol, meaning that an investigation had been performed with at least three sets of human subjects, plants, fungi or other organisms.

Included articles composed a total of 351 articles: 320 from the first count (160 from 2017 and 160 from 2019) plus 31 from the second count (20 from 2017 and 11 from 2019) from plant and related sciences and medical sciences. Preliminary studies had shown that similar
numbers could show differences between the sciences. The survey PICOS question is given in the Introduction and involved a search for the four protocol options given above.

(a) **Electronic sources.** Electronic sources were: Journal Citation Reports (https://jcr.incites.thomsonreuters.com, 2017 and 2019 lists; for 2017 search: date first searched: October 2018; data last searched: March 2019; for 2019 search: date first searched May 2019; date last searched: October 2019. Google (https://scholar.google.com).

(b) **Journal search strategy.** Journal grids were created from Web of Science JCR lists (Supplemental Tables S7:S10: list criteria at top of table). A wide range of medical and plant studies were included for all surveys, but plant surveys excluded ecology journals and medical surveys excluded neurology journals, to ease decision-making.

Journals were published in 2017 or 2019 in English with journal search start points (initial grid points) distributed as evenly as possible within each impact factor (IF) range from 1 to 3 and then > IF4 (full grid criteria given in Supplemental Tables S7:S10). The exact methods used for the distributions of start points are given in the journal screen section of Fig 1.

Journals were included if they contained mostly articles ("mostly" defined as when, on first encounter with the journal, the first 10 articles did not contradict the criterion) which conformed to the article inclusion criteria (given below), with primary research, full articles available (or Abstracts with p-values), without rare subjects (defined below). If the start point journal did not conform to the inclusion criteria then an upwards or downwards shift was chosen at random (or for > IF6.5 a downward shift) and adjacent journals in the grid were assessed until a journal was found which did conform. (Ecology journals were excluded but no distinction was made between ecological and other studies from plant science journals).
Note there were missing outcomes because journals not freely available were not covered by the assessment.

(c) Article search strategy. Articles were included in the first count if they were original articles with at least one statistically-significant p-value comparison for a main result concerning categorically distinct groups. Medical articles had to have human subjects; plant articles either plants, fungi or other small organisms. Included and excluded articles are all given in supplemental files. The first count counted protocol options 1) to 3) from the Survey section above and a second count, which utilised articles excluded from the first count by replacement, counted protocol option 4) and also meta-analyses.

Articles were from different journals apart from, necessarily, plant journals ≥IF3.55: in these ≤3 articles per journal were surveyed to make up required numbers of articles (see grids, Supplemental Tables S7:S10).

Articles (or part-articles, see below) were excluded from the first count (partly for the sake of simplicity) with "pilot studies", cases, reviews, simulation or modeling, technical methods, studies involving rare subjects, phased clinical trials, all -omic type studies (e.g. genome-wide association studies, RNA expression arrays), all genetic diversity, taxonomic, population structure, selection or evolution studies, cells from multicellular organisms or produce, diseases or conditions defined as less than 1 in 2000 human prevalence or incidence. (Neurology studies were excluded for ease of decision-making.) If no suitable articles were found within 10 articles, then the main reason was noted in the grid and the next journal was assessed. Above impact factor 3.5, especially with plant articles, many studies were multifaceted with many sub-studies and the exclusion criteria were applied to sub-studies selected (and stated in the column ARTICLES in the survey after the reference).
Article selection (with random start points: random numbers created using R function `runif()`) was carried out by two authors (AB and KP by joint decision), and checked by two authors (JSCC and TW). Disagreements were resolved by the referee (AC). No data was extracted from overlapping or duplicate reports. The risk of bias in article selection was minimal as the inclusion criteria included a wide range of possible articles. The risk of uncertainty in determining protocol was given for each article included (see Supplemental Tables S3:S6) as: 1) Risk: Main result = risk that comparison was not for main result. 2) Risk: Repetition = how unclear was the number of times of replication; 3) Risk: Repetition of p value = how unclear was the number of times of replication of p-values (to decide between a triple-result or global protocol).
Web of Science JCR lists: 2017 and 2019. SCIE, SSCI Categories. Available at https://jcr.incites.thomsonreuters.com. Lists also available in journal grids in supplementary files S7:S10. Total numbers available (impact Factor ≥1):

2017: Medical journals, n = 211; Plant journals, n = 215.
2019: Medical journals, n = 2073; Plant journals, n = 230.

**Journal screen:** Accessible journals chosen spaced evenly according to impact factor (IF): 20 journal screen start points distributed for integer intervals from IF1 to IF3 and ≥IF4. Random shifts (except ≥IF6: downward shifts) used until included journal selected (all start points and shifts shown in journal grid supplementary files).

Journals selected: n = 290; Totals: medical n = 160; Plants n = 130; 2017: Medical n = 80, Plants n = 67; 2019: Medical n = 80, Plants n = 63.

**Article screen:** Started at random month and random standard research article (using random numbers 1:12), continued downwards and cycled until article with inclusion criteria found. For plants >IF3.5 ≤3 articles from each journal were necessary to make up numbers (necessitating cluster chi-squared analyses).

Articles selected: n = 351: 1st count: 2017: Medical n = 80; Plants n = 80; 2019: Medical n = 80; Plants n = 80. 2nd count: 2017: Medical n = 6; Plants n = 14; 2019: Medical n = 6; Plants n = 5.

**Articles assessed for eligibility:** n = 713. 2017: Medical n = 171; Plants n = 197. 2019: Medical n = 176; Plants n = 169.

Research articles with humans or plants/fungi/other organisms. **Excluded:** phased clinical trials, pilot studies, reviews/cases, modeling, family relative studies, epidemiological studies, rare diseases with <1/2000 individuals, novel transgenic plants. **Included:** at least one significant p-value for a main result; 2nd count (utilising articles excluded from 1st count by replacement): results with replication errors (see text) and meta-analyses.

**Articles excluded:** n = 362 (1st and 2nd counts together):

2017: Medical: n = 85; Plants: n = 103;
2019: Medical: n = 91; Plants: n = 83;

**Studies included in synthesis: n = 351** (1st and 2nd counts together):

2017: Medical n = 86; Plants n = 94;
2019: Medical n = 85; Plants n = 86.

Studies included in quantitative synthesis/analysis: n = 351; 2017 n = 180; 2019 n = 171. Cluster-adjusted chi-squared tests between sciences for defined protocols, or Fisher exact tests.

Figure 1. PRISMA Flow Diagram.
(d) Definitions. Some definitions are given in Table 1, or are further refined here:

**Repetition.** Repetition (biological) was defined as either in time, space or with groups of organisms (with no other differences relevant for the comparison made), in that the whole investigation for the comparison being evaluated occurred more than once, including a new set of plants (or other organisms) for the "plant science" survey, or humans for medical research, within the same article by the same research group. In some cases it was clear that repetition had been performed using, for example, three species of the same group or three related genes modified to show the same effect: these were also included as repetition if the fact that different species or genes had been used was not relevant to the comparison investigated. A complication arose for genetically modified organisms: standard production uses three independent experiments producing only three individual organisms (defined here as rare). However later each line might have many plants/individual organisms, and it is a difficult question as to how many individuals, how many lines, and how many repetitions of an experiment should be included in order to sufficiently account for biological variation. Here, genetically modified organism studies were included if they had been produced in a previous study.

**Non-replicated protocol.** Declared if no evidence of replication was discovered in an article with a partial positive result (with a p-value). Note these could also feed into random-Institutes protocols (see definition below).

**Random-Institutes protocol.** This refers to a protocol in which a non-replicated study is published, followed by reproduction by random Institutes, followed by meta-analysis (other higher-level evidence protocols not considered). These were not assessed directly in the present article and meta-analysis prevalence is only given for reference.
Replication-error protocol. Declared if replication errors (i.e. standard errors or deviations among replicates) were found with no p-values given (or other measure) for random error direct assessment.

Global (triplicated or duplicated) protocol. Declared if the study was clearly duplicated or triplicated, but no p-values (or results below significance level) given for individual replicates i.e. p-values were only given for global results (this was declared as default if doubt arose concerning triple or double-result protocols). Use of one of these protocols counters systematic errors by assessing either 1) if replicate had significant effect or 2) whether interaction occurred between replicate and main effect. Note this is not as strong as a triple-result protocol and, additionally, usually a significance level (effectively for pooled results) of p<0.05 was used.

Triple (or double)-result protocol. Declared if the study was clearly duplicated or triplicated and p-values (or results below significance level) given for individual replicates. Note that global results and p-values could also be given, but the point is that results have also been found in individual replicates independently i.e. not only has the study been replicated (with pooled results) but also consideration has been made as to whether the result was found in individual replicates. This gives a much stronger counter to systematic errors than global protocols. The standard significance level for a triple-result protocol was usually p < 0.05 three times and therefore random error was countered by a non-replicated-equivalent significance level of p<10^{-4} or less, as discussed.

(e) Reporting and analyses. Reporting followed PRISMA guidelines (Fig 1). The exact PICOS question addressed is given in the Introduction. Note that this was a results-based assessment (not an assessment of stated intent) and, as far as we know, no review protocol exists for such a survey. All Supplemental files are found at https://github.com/Abiologist/Significance.git.
(B) Statistics. All statistical calculations used the R statistical platform version 4.0.3 (2021; (28)), using two-tailed tests. Cluster-adjusted chi-squared tests (R [htestClust] chisqtestClust, (29,30); Supplemental_files_S11:S13) were performed to compare proportions of articles with triplication (triple-result plus triplicated global protocols together) within the plant and medical sciences. Fisher's exact tests (without adjustments for clustering) compared prevalence distributions of: triple-result, triplicated global result, double-result, duplicated global result and non-replicated result protocols between the two sciences. The significance level was set at \( p = 0.01 \), twice.

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Supporting information

S1 Supplemental TABLE_EXAMPLES_PHYSICS_2017-2021 S1.xlsx

S2 Supplemental TABLE_EXAMPLES_PLANT_SCIENCES_1980-1999 S2.xlsx

S3 Supplemental TABLE_SURVEY_MEDICAL_2017 S3.xlsx

S4 Supplemental TABLE_SURVEY_PLANT_SCIENCES_2017 S4.xlsx

S5 Supplemental TABLE_SURVEY_MEDICAL_2019_S5.xlsx

S6 Supplemental TABLE_SURVEY_PLANT_SCIENCES_2019 S6.xlsx

S7 Supplemental TABLE_Medical journal grid 2017 S7.xlsx

S8 Supplemental TABLE_Plant journal grid 2017 S8.xlsx

S9 Supplemental TABLE_Medical journal grid 2019 S9.xlsx

S10 Supplemental TABLE_Plant journal grid 2019 S10.xlsx

S11 Supplemental chi-squared tests S11.docx

S12 Supplemental TABLE_Clusters_2017 S12.xlsx
