**The Fault lies in our Stars not in Ourselves:
Randomized Controlled Trials and Clinical Knowledge?**

**David Healy – August 2020**

**Executive Summary**

As a matter of the historical record, randomized controlled trials (RCTs) stumbled into being without a coherent clinical underpinning. I don’t agree, see Fibiger 1898 and streptomycin trial 1948. The clinical situation was the same, the only difference being randomisation

RCTs have proliferated for reasons of bureaucratic convenience rather than epistemological coherence. No. See just above. Randomisation is the only method that prevents against systematic differences between two groups

Elements of RCTs, such as randomization, confidence intervals, and primary endpoints, can help in treatment evaluation but their indiscriminate combination can cause problems.

Pharmaceutical company use of RCTs for regulatory and marketing purposes gives rise to another set of problems distinct from the ones outlined here.

The rhetoric pitching RCTs as offering gold-standard evidence misleads as regards both treatment hazards and benefits

Treatment induced morbidity and mortality is rising, possibly driven by the use of RCTs as our primary treatment evaluation tool. Interesting hypothesis

**In the Beginning**

In 1947, a trial of streptomycin introduced RCTs to medicine. See attached. A member of my family, Fibiger, was 50 years ahead of this, although he used the alternate day method. His trial is brilliant. From then, through to their incorporation into the 1962 amendments to the US Food, Drugs and Cosmetics Act, occasioned by the thalidomide tragedy, doubts were expressed as to whether RCTs had a solid epistemological basis in clinical reality. See Schwartz and Lelouch about pragmatic trials, which also Peto has advocated for many yearsSince then there have been ongoing disputes about the best statistical approach to take to RCT data – whether confidence intervals are preferable to significance testing, for instance. There have also been efforts to account for a heterogeneity of treatment effects (HTE) within the wider Evidence Based Medicine (EBM) movement, which touch on the issues raised here (Kravitz et al 2004). But few doubts have been expressed about the fundamental validity of RCTs.

Repeated characterizations of this form of trial as offering gold-standard evidence likely leave most clinicians thinking RCTs have a solid epistemological don’t use this word, leads readers astray. It is not about epistemology if you to as usual, apart from randomizing foundation, even as they recognize difficulties in translating from population or average effects to individual patients. If clinicians have no apparent qualms, few others likely feel compelled to dig deeper. Even those who recognize problems accept a characterization of RCTs as generating evidence that is generalizable and knowledge that lies within confidence limits in contrast to the views of clinicians and case reports.

**Hill and Fisher**

A Medical Research Council (MRC) trial of streptomycin in 1947 tested the feasibility of randomization as a further control of the subtle biases involved in evaluating a medicine. This RCT demonstrated that randomization was feasible but the information it produced was less clinically relevant than a prior trial of streptomycin that controlled for confounders in the then standard way which way, explain? What was the effect, compared to the trial? Too big? and depended on clinical judgement (Healy 2012; Healy 2020). The standard trial noted important therapeutic issues the RCT missed - streptomycin could cause deafness and tolerance developed rapidly.

Austin Bradford Hill, the MRC trial lead, did not consider the epistemological validity of RCTs. He had taken the idea of randomization from a horticultural thought experiment Ronald Fisher outlined two decades previously in which Fisher proposed that randomization could control for unknown confounders. Hill’s idea was that it might control for the difficult to detect ways in which clinicians steer patients likely to respond well into an active treatment arm. There was no consideration as to whether randomization would control for the unknown of doctors not knowing what they were doing (Healy 2020). This sentence does not make sense

RCTs brought statistical significance tests in their wake because Fisher tied randomization to significance testing. The only things that can interfere with expert judgement not being correct every time, Fisher argued, are unknown confounders and chance. Significance testing could control for chance and randomization could control unknown confounders. Fisher’s model had an anchor in the real world –experts who knew what they were doing and whose judgements were invariably correct – such as offering a view that wearing a parachute if you jump from a plane at 5,000 feet will save your life. For Fisher, experiments were a way of demonstrating that we knew what we were doing this does not make sense to me. If we knew, no experiment is needed rather than a leap into the unknown - they should get the same result every time.

There are situations in medicine, where doctors know what they are doing. The more they know, the more they approach Fisher’s expert, but no one runs randomized trials in situations where we are likely to get the predicted result every time. There are thousands of superfluous repetitions of trials where we know very well what we will get, and many of these are therefore unethical, e.g. if there is a placebo

In the case of breast cancer, on the basis of advances in physiology, it was hoped that giving Herceptin to women with Her 2+ receptor breast cancers might produce better responses than cisplatin, a more indiscriminate toxin, which nevertheless extends longevity compared to placebo. Trials confirm this but also reveal that even using Herceptin in Her 2+ breast cancers, we do not get the same result every time – there is a lot we don’t know.

Our lack of knowledge is even more marked in trials testing stents compared to other cardiac procedures, where doing what seems obvious does not produce the expected results. The issue is not whether stents work or not but whether we know what we are doing, which we mostly don’t. While recent stent RCTs are a good demonstration of the power of RCTs to stall a therapeutic bandwagon, explain what you mean the view that clearing blocked arteries might not produce a good outcome had been accepted clinical wisdom in vascular leg surgery for decades and for stents in some quarters before any RCT had been run.explain that stents do not decrease mortality, be more straightforward, please

**Confidence Intervals**

Taking issue with Fisher’s real-world anchor - an expert knowing what they were doing - Jerzy Neyman and Egon Pearson borrowed from Carl Friedrich Gauss’ use of confidence intervals to manage the error in astronomical measurements of stars. Gauss’ ideas were picked up by Pierre-Simon Laplace and their combined input (1809-1827) to the central limit theorem, least-squares optimization and efficient linear algebra provided celebrated benefits for the physical sciences, engineering, astronomy, and geodesy. When applied to the problem of imprecise measuring instruments and invariant entities like stars, confidence intervals have an anchor in the real world, helping us to decide if our varying measures reflect the presence of one or two stars.

Confidence intervals unquestionably work but are not necessarily valid in clinical trials. Taking successive measurements of a pulse perhaps not a good example, as pulse is not constant like a star is in an individual is similar to determining the precise location of a star – the tighter the confidence interval bounding our measurements the more apparent we can do things reliably. Using confidence intervals to describe data also make it less likely we will reject a drug like Herceptin just because we don’t get the same result every time.

Confidence intervals could be used in a manner consistent with their use in astronomy to distinguish between a repeated set of pulse measurements before and after administration of a drug - to one individual. The current use of confidence intervals in RCTs seems predicated on the idea that a cohort of patients in standard parallel group trials can be regarded as a single object like a galaxy. But pulses can increase in response to a drug in one individual and decrease in a second in response to the same drug – this is not measurement error.

Claiming the true effect of the drug likely lies near some mean of the effects in a group of individuals, potentially giving us a best estimate of no effect no effect?, is wrong. When a mechanism to decide whether there are one or two stars present turns up the answer there are none, something has gone wrong. Distinguishing between Average Treatment Effects (ATE) and HTE drop abbreviations, I have forgotten what HTE is recognizes but doesn’t solve this problem. A series of trial designs have been proposed to mitigate the problem, with some recognition that the degree to which the problem can be mitigated depends on how often individuals respond in opposite ways – if commonly the notion of average treatment effects falls apart. Streptokinase in AMI depends on time since pain started, becomes harmful after about 17 hours (Peto), you could use that example. In the case of stars, we knew enough about what we were doing to make reasonable inferences from varying measurements. We need to know as much to make comparable inferences when giving medicines.

**Primary Endpoints**

There is a deeper problem than just how commonly people react differently. Fisher’s significance testing, and Gauss’ confidence intervals, require a focus on a primary endpoint – are there one or two stars or more or less ears of corn? In medical RCTs, as currently undertaken, a focus on a primary endpoint is viewed as key to ensuring that only chance or measurement error will get in way of the correct result. These are different issues, e.g. there can be several endpoints This rather than the use of confidence intervals or significance testing per se limits the value of RCTs in medicine.

A horticultural expert focused on whether a fertilizer improved corn yield would likely have no more accurate a view of its effects on worms in the ground or insects in the air than a non-horticulturalist - in respect of whose views significance testing by Fisher’s definition would not be appropriate.

Similarly, Gauss’ confidence intervals applied to an astronomer’s measurements of the location of a star are of little use when it comes to pinpointing the trajectories of satellites crossing the path of the observations.

There is something of an assumption that the primary endpoint in an RCT is the commonest effect of a drug. Not the assumption. Death is not common but can be primaryTreatment heterogeneity leading to wider confidence intervals than are ideal can be accommodated against this background as can missing other effects assumed to be rare or not appearing within the duration of the trial. But RCTs are often not trained on the key or commonest thing a drug does. The commonest effect of an SSRI is genital anesthesia, which appears almost universally and within 30 minutes of taking a first pill. It should not be possible to miss it, but this effect has been missed in all never say all as you have not read all of them RCTs of these drugs for nervous conditions because of an RCT required focus on a primary endpoint. A focus on a primary endpoint is essentially an act of hypnosis that likely routinely leads to common treatment effects being missed entirely. These are likely your strongest points

RCTs can help evaluate one effect of a drug but are a poor method to evaluate a drug’s overall effects. This is not an inherent limitation but is caused by the way the trials are done, they could be done very differently The precision focus on a primary endpoint means we might end up being able to say a lot about a pimple but very little about the person on whose back it is. Casting RCTs as offering gold standard evidence about a drug creates an ignorance about the ignorance they generate.very good point

A negative result in an RCT may temper the enthusiasm for an apparently obvious course of action such as stenting coronary arteries but the stent trials do not provide a basis for dismissing a link between an apparently good outcome in an individual case after stent insertion. The trials demonstrate we do not know what we are doing in general; there may be a subset of patients in which a stent is the correct answer. In an ideal world, the greatest utility of treatment RCTs would not lie in their giving us the right answer but that a negative result should force believers in a treatment to delineate a patient group who clearly benefit. I totally disagree with this. Do not speculate about stents being good for some patients. I doubt they are. They can be lethal. Drugs should be preferred for angina. See what I have written about my own experience as a patient, I only escaped a stent because my coronaries turned out to be totally normal when I was put on the operating table!!

RCT evidence should never trump an evident effect that appears after treatment. You are too sure here. The evident (what is that) may not be so obvious that RCT are not more reliable, observers postulate a lot that never happened eg. UFOs, to follow your universe allegories If a person becomes suicidal after taking an antidepressant, the issue of what is happening in that case is a matter of assessing the effects of their condition, circumstances, prior exposure to similar drugs, dose changes on the medication and whether there are other evident effects of treatment consistent with a link between suicidality and treatment. Unless RCTs have been designed specifically to look at the effects of treatment on a possible emergence of suicidality (and there have been none, as far as I know), RCT evidence is irrelevant. NO, not irrelevant, see Hengartner and a lot else. They did show increased suicides.

**Confounding by Ignorance**

In the case of RCTs, inconvenient results often come with a rider that confounding by indication may make their interpretation difficult. This translates into a caution against assuming a treatment is causing a problem. Many clinicians and the wider public will not be clear why randomization does not take care of confounding by all unknown unknowns – such as confounding by indication. Re-designating this as confounding by ignorance may better convey why not.

Consider two scenarios involving the antidepressants, imipramine and paroxetine. Imipramine was discovered in 1957 and launched in 1958 without any RCT input. Among other actions, it is a serotonin reuptake inhibitor. In later RCTs it (and other older antidepressants all discovered and marketed without RCTs), “beat” SSRI antidepressants in trials involving patients with melancholia (severe depression). Melancholic patients are 80 times more likely to commit suicide than mildly depressed patients.

By 1959, clinicians noted that imipramine, wonderful though it was, could cause agitation and suicidality in some patients that cleared when the drug was stopped and reappeared when restarted – Challenge-Dechallenge-Rechallenge (CDR) proof it causes suicide.

In an RCT of imipramine in melancholia, a drug that can cause suicide, imipramine seems likely you are speculating, it has never been shown that this drug or similar ones reduce suicides. I advice you to drop this to protect against suicide on average by reducing the risk from melancholia to a greater extent than placebo. In contrast, in the RCTs that brought SSRIs to the market, these drugs doubled the rate of suicidal acts. This was because SSRIs are weaker than imipramine and had to be tested in people with mild depression, at little risk of suicide. The low placebo suicidal act rate revealed the risk from the SSRI – as it does for imipramine put into trials of mild depression I don’t think we have such data for imipramine?. RCTs can, in other words, mislead as regards cause and effect – potentially getting results all the way along a spectrum from “causes”, to possible risk, likely protective and “cannot cause”.

In any trial where both condition and treatment cause superficially similar problems, as when antidepressants and depression cause suicidality or bisphosphonates and osteoporosis both lead to fractures, a dependence on RCT data rather than clinical judgement risks misleading. clinical judgement is far more misleading, especially in psychiatry!!This is likely the case for a majority of RCTs in clinical conditions, which are Treatment Trials rather than Drug Trials. What is the diffence?

Drug Trials are also done on healthy volunteers, and in these, which ordinarily do not have a primary endpoint, treatment effects stand out more clearly. SSRI Drug Trials demonstrated sexual effects were common, often debilitating, and might endure after treatment stopped, that agitation up to suicidality was common and that dependence commonly occurred after exposures of two weeks I do not think two weeks is common, it usually takes longer to become dependent. The “correct” choice of primary endpoint in subsequent Treatment Trials could eliminate these effects – provided the non-confidential Drug Trial data remained unpublished.

Paroxetine was later put into Treatment Trials of patients with Major Depressive Disorder (MDD) and patients with Intermittent Brief Depressive Disorders (IBDD). IBDD patients (borderline personality disorder) are repeated self-harmers. Their depressive features, however, mean that IBDD patients can readily meet criteria for MDD.

In April 2006, GlaxoSmithKline (GSK) released RCT data showing MDD patients had a worrying increase in suicidal event risk on paroxetine (Table). The data from IBDD RCTs in the GSK release were better. We can add 16 suicidal events to the paroxetine IBDD column and still get an apparently protective I cannot see that rather than problematic result for paroxetine when MDD and IBDD data are added together.

**Table: Suicidal Events in MDD & IBDD Trials**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Paroxetine** | **Placebo** | **Relative Risk** |
| MDD Trials Acts/PatientsIBDD Trials Acts/PatientsCombined Acts/Patients | **11/2943****32/147****43/3090** | **0/1671****35/151****35/1822** | **Inf (1.3, inf)****0.9****0.7** |

This effect has been noted as a hazard of meta-analyses and is termed Simpson’s paradox but it has to apply to some extent in every trial that recruits patients who have a superficially similar but in fact heterogenous condition such as depression, pain, breast cancer, Parkinson’s disease or diabetes – almost all medical disorders. The issue here is our ignorance about the heterogeneity of conditions rather than an additional HTE problem.

Every time there is a mixture of more than one patient group in a trial, randomization will ensure some patients hide some treatment effects I do not understand the mechanism, please explain – good and bad. Trials of standard treatments for back pain, for instance, will mask the beneficial treatment effects of an antibiotic on back pains linked to infections (up to 10% of back pains). It will often be possible to design a Treatment Trial that uses an effect a drug causes to hide that same effect. I do not get the point

This confounder applies to placebos. The assumption is that in Treatment Trials placebos simply control for natural variation I do not agree, they are mainly used to blind trials. But placebos can have potent treatment effects, this is not correct, see our review of placebo making them another treatment like an antibiotic in the backpain scenario above. We do not know enough about placebo responses to know whether in the context of randomization they control or confound the data.

Every medicine no, cancer drug are approved without placebo that gets on the market, by definition, beats placebo (often inconsistently). As a result, it has become unethical to use placebos in clinical practice, when for some patients it is possible to do open heart surgery on placebo what?? Philiphine magicians and fraudsters or what? and for those for whom it works more generally a placebo may be a better idea than therapeutic poisoning. Caring for people is not placebo, please be careful here

Another problem is that a quantitative approach to data generated by algorithm ?? and RCT is not an algorithmrather than an approach based on judgement increases the risk that minor events in a placebo arm will be offset against significant events in an “active” treatment arm offering an opportunity to claim that nothing specific has happened, when it has. This is more a sample size (power) issue

**“Side” Effects**

The suicidality, sexual dysfunction, agitation, or insomnia caused by antidepressants in clinical trials are commonly folded into a primary endpoint, a score on the Hamilton Depression Rating Scale (HDRS), which includes questions on suicidality, sexuality, sleep and agitation. These changes render confidence intervals around scores on these items meaningless, compromise the use of the scale more generally, and risk hiding a benefit. The opposite seems more likely, the scale suggest a relevant effect when there is none!

If registered on adverse event forms, treatment emergent suicidality or sexual dysfunction should almost de facto be causally linked to treatment. But investigators are forced to tick boxes as to the likelihood of a link, including possibly unrelated, toward which the ethos of RCTs, which aims at replacing clinical judgement with decisions based on an analysis of datapoints rather than an interrogation of people, steers them. I write this in my vaccine book:

The review also mentioned a large trial that compared 9-valent Gardasil with 4-valent Gardasil in 14,215 women.75 In this trial, there were far more serious local reactions with the 9-valent vaccine (e.g. 272 vs 109 cases of swelling). A supplementary appendix revealed that there were also more serious systemic adverse events in girls receiving the 9-valent vaccine than in those receiving the 4-valent vaccine (3.3% vs. 2.6%, p = 0.01).74,75 The number needed to harm was only 141,75 and it would undoubtedly have been even smaller if the control group had not received Gardasil, too.

This result suggests that, contrary to EMA’s reassuring messages, adjuvants are harmful, not only locally, but also systemically. Gardasil 9 contains 500 μg of the AAHS adjuvant whereas Gardasil 4 contains only 225 μg.75 Yet only 4 of the 416 serious adverse events were judged to be vaccine-related by the trial authors.75 It is “interesting” when clinical investigators – many of whom had many conflicts of interest with vaccine manufacturers - decide that only 1% of the serious adverse events are vaccine-related. Where did they publish this? In *New England Journal of Medicine* of course, which one of my colleagues has dubbed *New England Journal of Medicalisation*. And how could they make such a decision when both groups received Gardasil? It just cannot be done.

The question of whether the suicidality the patient in front of me is experiencing comes from their illness or their treatment is not a matter of deciding if there are 1 or 2 stars. In this case, we already know there are two stars and a lot about them. Instruments specifically designed with the characteristics of each star in mind may facilitate the distinction, but ultimately it’s a case of pattern recognition and a judgement call – with one call leading to an increase in the dose of treatment and the other leading to a reduction. Oh my God no David! It has not been demonstrated that any dep pill reduce suicide. It is a terrible mistake if you increase the dose based on your clinical judgment. The high stakes may make the option of falling back on an algorithm appealing – but it is not good science or good medicine.

In 1959, clinicians could readily distinguish between a treatment emergent suicidality on imipramine and the suicidality caused by melancholia. This is simply not true In 1961, Frank Ayd, the discoverer of amitriptyline could distinguish the sexual dysfunction it causes from the sexual dysfunction melancholia causes. Through to 1991, clinical knowledge of drug effects derived primarily from clinical experience, embodied in case reports and published in clinical journals. The steady rise of mechanical evaluations, however, allied to a sequestration of trial data, has relegated clinical evaluations that drug X causes effect Y, even when buttressed by evidence of CDR???, to the status of anecdotes. From 1991, journals stopped taking anecdotes about “side” effects that almost by definition are rare compared to the treatment effect; I am pestered all the time by editors who ask me to submit case reports to their case report journal the bad luck of a few patients is not viewed as deserving to be weighed in the balance against science.

As a result, where in the 1960s the harms of treatments took at most a few years to establish after a drug came on the market, by 1990 a set of processes were in place that mean it can now takes decades for the harms of treatments to be established, it also too decades before dependency on benzos was accepted, from the 1960s as for instance in the case of impulse control disorders on dopamine agonists or persistent sexual dysfunction on isotretinoin, antibiotics, analgesics, finasteride and other drugs.

This growing delay underpins a perception that pharmacovigilance is in crisis. Proposed solutions mention the need for systems to detect the rare effects of treatments not found in RCTs. There is a turn to a mining of electronic medical records or other observational approaches. New signal detection methods and investigative approaches are always welcome, but these are not the answer to the problems we now face, which lie not primarily in a failure to detect rare effects but in a systematic failure to acknowledge common effects. Drug Trials are a better way than any new signal detection method to detect these common effects.

The tendency, not ability of RCTs to focus on one effect suits trials testing for an effect of possible commercial interest. But this focus does not suit an evaluation of treatments, the intention of which is to poison or mutilate in the hope of producing an overall benefit. Studies run on a primary endpoint chosen for commercial reasons cannot be expected to produce the kind of information that might inform therapeutic poisoning. Can we expect data-handling methods developed for fertilizers and stars to encompass the complexity of therapeutic poisoning?

Commercial trials produce regulatory pronouncements that a treatment’s Risk-Benefit ratio is favorable. A favorable Risk-Benefit ratio never use this.

# Benefits and risks of drugs

This terminology is misleading, as it implies that drugs always have benefits but not necessarily any harms, only risks of harms. It is the other way around. Drugs always cause harm and sometimes they also cause benefits. Thus, a more appropriate terminology would be possible benefits and certain harms, and since the harms are certain, they should be flagged first: certain harms and possible benefits. Many years ago, I advocated for a change in terminology, both in CONSORT and Cochrane, and this was accepted so that the recommended terminology now is: What is the balance between benefits and harms? Unfortunately, many people use the construct benefit-harm ratio, which is only meaningful if benefits and harms are the same, e.g. total mortality, which is very rarely the case. In all other cases, it will be subjective and arbitrary what people think of the balance according to the values they attach to various outcomes and how common they are.

Further, benefits and harms cannot be a ratio, as they are not measured on the same scale.

here implies there is a balance in which all benefits and harms can be weighed. There is no balance, and there is no weighing. One statistically significant effect is taken to count for more than all other effects, even serious effects that occur more frequently and can include death, but which by design are not significant. Non-sign difference in mortality are not only ignored but deaths are underreported as well,

Hughes S, Cohen D, Jaggi R. Differences in reporting serious adverse events in
industry sponsored clinical trial registries and journal articles on antidepressant
and antipsychotic drugs: a cross-sectional study. BMJ Open 2014;4:e005535.

**Objectivity**

Concerns about what is often termed the population effects of RCTs and the mismatch between these and the apparently “anomalous” responses of individual patients has been framed in terms of HTE and recognized in EBM as needing an incorporation of RCT evidence into the judgement of clinicians and the values and preferences of patients.

The argument here is that RCTs, as they have evolved RCTs, are essentially algorithmic or operational. DSM criteria in mental health, and the metrics for blood pressure, peak flow rates and bone densities are similarly operational. The creators of the DSM criteria claimed that “of course just ostensibly meeting criteria for an illness doesn’t mean the person has the illness” I would like to know where they write this; this is important – clinical judgements are needed to establish what is really going on in the case of criteria, just as they are in the case blood pressure, peak flow or bone density metrics. In practice, however, operational exercises like RCTs, DSM criteria and many medical metrics nudge us toward a suspension of judgement and put a third party like the pharmaceutical industry in a strong position to contest any introduction of judgement by a doctor or patient on the basis that the figures are demonstrably more objective than any clinician or patient judgement can be

Science traditionally generates data and challenges us to interpret them. New techniques (like a new drug) can throw up new observations, but while new data can challenge prior judgements, the mission of science has not been to replace judgement by technique.

Individual judgement of course is suspect. This argument does not advocate replacing collective evaluation by a reliance on individuals or doctors; the argument is for collective evaluation rather than its replacement by algorithmic I think this is a wrong word to use that detracts from your arguments processes. Collective evaluation has a clear footing in the real world, as the streptomycin trial demonstrated; the idea that RCTs have as clear a footing has been assumed rather than established. Contradictory as it was a trial

Arguments stressing the need for RCTs rather than clinical judgement point to a small series of treatments, oh no, there is a lot else such as internal mammary ligation, that RCTs demonstrated did not work, with the implication that clinical judgement can get things wrong. The RCT in this case was only run because the dominant clinical judgement was that these treatments didn’t work – an article in the Reader’s Digest notwithstanding.???

These arguments fail to note that most of the current treatment classes we have were introduced in the 1950s without RCTs. That the treatments introduced then from anti-hypertensives and hypoglycaemics to psychotropic drugs are more effective than treatments introduced since. I do not think we can say this. A lot of garbage also appeared before we used RCTs That RCTs facilitate the introduction of treatments with lesser effects.

The response to the point about weaker treatment effects is the same as the response to anomalous effects – namely that RCTs give population or average treatment effects. This implies a valid population with individual outliers, when in fact there is no knowing how ***any*** individual will respond to an antidepressant for instance. Bad example, as the SSRIs do not have relevant effects on depression Fisher expected us to get the same result in every individual case, and within limits confidence intervals offer the same guarantee. Neither Fisher nor Gauss would recognize a problem in translating from a “population” to an individual level. But we need RCTs to find out if treatments work on average. This is not a valid criticism of RCTs. We are in a much better position when using clinical judgment if RCTs have been doneBecause of diagnostic imprecision, individual heterogeneity, treatment effect heterogeneity, and other factors we don’t have valid populations. To adapt Shakespeare, the fault here lies in our stars not in ourselves.

Clinical practice is essentially a judicial rather than an algorithmic exercise. The view offered here is that our best evidence as to what happens or is likely to happen on treatment lies in the ability to examine and cross-examine the person or persons (interrogate the data) given that treatment. Every day of the week doctors and patients continue or stop treatments based on judgements as to whether the treatment is working or not. These judgements have to be mostly correct or else medicine would not work. This is not correct. Clinicians,, particularly in your own specialty, are led astray every day by their observations: my patient improved when I gave this drug, ergo the drug worked. This is as bad as it gets.

But what holds true at the individual level must be true at the population level also. The evaluation of a treatment must be judicial rather than algorithmic. This can rarely be done and you contradict yourself. When many drugs with minimal effects (if any, could just be bias, e.g. drugs against dementia do not work at all) are put on the market, it is totally impossible for clinicians to judge if a certain drug has worked in a certain patient (e.g. with dementia).

An endorsement of clinical judgement does not suit health service managers or the pharmaceutical industry, it surely does, see your own specialty where all improvements are ascribed to the drugs for whom the supposed generalizability of RCT knowledge and confidence intervals that can be offered for such knowledge are legally appealing.

Behind these problems lies the undefined concept of clinical data. This paper takes the position that data means the people entered into a study - the people who lie behind any table of figures or behind the outcome of any analytic process applied to those figures. At present case reports with names attached are the only form of controlled clinical investigation that offers access to the data, the possibility to interrogate the data and, accordingly, an opportunity to ground any conclusions in the real world. This section is not clear

**The Place for Randomized Controlled Trials**

RCTs are an important tool to evaluate certain drug effects rather than a means of generating gold-standard knowledge about drugs or treatments.

They came into widespread use after 1962 on the back of claims by Louis Lasagna and Walter Modell they might solve a regulatory problem – not because of their epistemological validity or proven superiority to other methods of evaluation (Healy 2012; Healy 2020).

In 1965, Tony Hill offered the view that RCTs have a place in the study of ***therapeutic efficacy,*** but they are only one way of doing so and any belief to the contrary was mad (Hill 1965).

The subsequent history of company trials demonstrates that the knowledge derived from RCTs is far from generalizable. In 1962, when two positive placebo-controlled trials were put in place as the criterion of entry to the market, it was assumed any subsequent trial would almost always replicate the result of a first two positive trials. This is clearly not the case. And FDA speaks about failed trials rather than failed drugs even when most placebo trials did not find an effect. From my June 2020 psychiatry book:

I have often encountered patients who are on the antiepileptic, lamotrigine. Only two positive trials were published for this drug, while seven large, negative trials were not.127 Two positive trials are all it takes for FDA approval and the agency regards the others as failed trials, even though we see a failed drug. You need to have a vivid fantasy to imagine what goes on at drug agencies, and the length to which they are willing to go to accommodate the interests of the drug industry.51 The bottom-line is that drug regulation doesn’t work. If it did, our prescription drugs would not be the third leading cause of death,128-138 and our psychiatric drugs would not have come close to record.4

Lasagna, the leading advocate for RCTs up to 1962, also changed his view, adding in respect of adverse events that while the common view was that spontaneous reporting was unsophisticated and not scientifically rigorous, this was only the case in the dictionary sense of sophisticated meaning “adulterated” and spontaneous reporting was in fact more worldly-wise, knowing, subtle and intellectually appealing than RCTs (Lasagna 1983).

Randomization, placebo controls, confidence intervals and primary endpoints all have a place in the evaluation of treatments. Confidence intervals are clearly appropriate in instances where measurement error is likely to play a part.

Randomization is an extra control on clinical bias. Not extra, it is absolutely essentialThere is a place for it, unhooked from primary endpoints and statistical significance, as happens in large pragmatic trials – but here the word pragmatic concedes our limited understanding of what we are doing.

There is a place for it in surgical studies of a time-limited intervention as opposed to chronic therapeutic poisoning, as well as in studies to evaluate programs, and treatment studies that have a hard endpoint – like all-cause mortality, but even here we risk being misled by findings of no change in mortality into missing a switch from cardiac events to cancers when many patients might preferred to die by a heart attack (Mangin et al 2007).

They have also shown that psychiatric drugs are pretty useless and harmful, David

RCTs also have a merit as a gateway to the market; randomization means that trials require less patients and can be run quickly. A positive result in commercial trials may indicate a compound has an “effect”. Trials aimed at establishing effectiveness, in contrast, require hard not necessarily outcomes and time. This is not a realistic gateway to the market. Demonstration of an effect, as with SSRIs for depression, means it is not correct to say this drug does nothing and on this basis entry to the market could be permitted.

By implication, the launch of a drug licensed on these terms would be the point when more comprehensive clinical evaluations should start, aimed at generating a clinical consensus as to the place of the drug in practice. As a general tool to evaluate the effects of a drug, RCTs should take second place to a group of experienced clinicians no, particularly not in psychiatry whose observations are not constrained by checklists and an investigation tailored to one effect.

After 1962, RCTs became the standard through which industry would make gold, As they proliferated, and became increasingly mechanical, the mantra that they provide gold standard medical evidence took hold. The ignorance of ignorance in claims that the only valid information on medicines comes from RCTs compounds a series of other factors that make RCTs a gold standard way to hide adverse events and encourage over-use of treatments.

It is appropriate to use RCTs to raise the bar to those who would make money from one effect of a drug given to people at their most vulnerable, but seasoned clinicians, allied to increasingly health-literate patients, are better placed than RCTs to determine cause in the case of the multiple other effects every drug has, especially effects such as sexual or suicidal effects of antidepressants, for instance, that need input from patients able to distinguish condition effects from superficially similar treatment effects.

Drug interventions (therapeutic poisoning) invariably harm; the hope is that some good can also be brought from their use. Evaluations by RCT harm (generate ignorance), but if used judiciously some good can be brought out of the ignorance they necessarily generate.

It is less likely that good will be brought out of ignorance if we rely solely on a data handling formula. Analytic methods can describe data but whether good comes from their use requires the kind of judgement calls that statistical approaches ordinarily make a virtue of side-lining. A recent study looking at 29 ways to analyze a dataset, generated from referees giving red cards to dark and light-skinned soccer players, demonstrated that different techniques can lead to a wide variation in results with none able to guarantee what is happening in the real world (Silberzahn, Uhlmann, Martin et al. 2018).

**Commercial RCTs**

Pharmaceutical companies run “RCTs” for regulatory and marketing purposes, and this may generate a belief that any problems with RCTs stem from a link to commerce.

The difficulty in recognizing adverse effects has for instance been compounded by company sequestration of clinical trial data and a ghost writing of the clinical literature that hypes the benefits and hides the harms of treatments, compounded by a regulatory willingness to avoid deterring patients from treatment benefits by placing warnings on drugs.

Clinical practice is also compromised by licensing indications and by guidelines. There are no drugs licensed to treat adverse effects. L-dopa? When a person becomes suicidal on an SSRI, there is no treatment licensed to treat this toxicity. Many clinicians wanting to help feel compelled to diagnose depression rather than toxicity but a depression diagnosis inevitably leads to treatment with an antidepressant rather than something more appropriate stopping the causal drug like a benzodiazepine, a beta-blocker or red wine.

Guidelines based on a ghostwritten literature without any access to trial data list treatment benefits, but do not usually tackle treatment harms adequately, and this contributes to their disappearance.

The incorporation of RCTs into a bureaucratic regulatory apparatus has introduced elements such as surrogate markers, which mean that in real life treatments may not show effectiveness consistent with RCT demonstrations of a treatment effect. Trials showing antidepressants work, for instance, bizarrely have an excess of deaths and both suicidal and homicidal events in their treatment arms compared to placebo.

Commercial trials have given rise to the idea of an abstract Risk-Benefit ratio which along with treatment effect sizes, the Number Needed to Treat (NNT) or to Harm (NNH) are not based in clinical reality. From my newest book:

### Number needed to treat is highly misleading

It is standard in psychiatric research articles to mention the number of patients that need to be treated (NNT) to benefit one of them. The psychi-atrists mention NNT all the time as evidence that their drugs are highly effective. But NNT is so misleading that you should ignore everything you read about it.

 Technically, NNT is calculated as the inverse of the risk difference (it is actually a benefit difference), which is very simple. If 30% have improved on drug and 20% on placebo, NNT = 1/(0.3-0.2) = 10. Here are the main problems:

First, NNT is derived from seriously flawed trials, with cold turkey in the placebo group, insufficient blinding, and industry sponsorship with selective publication of positive results and data torture.

 Second, NNT only takes those patients into account that have improved by a certain amount. If a similar number of patients have deteriorated, there would be no NNT, as it would be infinite (1 divided by zero is infinite). For example, if a drug is totally useless and only makes the condition after treatment more variable, so that more patients improve and more patients deteriorate than in the placebo group, the drug would seem effective based on NNT because more patients in the drug group would have improved than in the placebo group.

 Third, NNT opens the door to additional bias. If the chosen cut-off for improvement does not yield a result the company’s marketing department likes, they can try other cut-offs till the data confess. Such manipulations with the data during the statistical analysis, where the prespecified outcomes are changed after company employees have seen the data, are very common.4,51,101,184 My research group demonstrated this in 2004, by comparing trial protocols we had acquired from ethics review committees with the trial publications. Two-thirds of the trials had at least one primary outcome that was changed, introduced, or omitted while 86% of the trialists denied the existence of unreported outcomes (they did not know, of course, that we had access to their protocols when we asked).184 These serious manipulations were not described in any of the 51 publications.

Fourth, NNT is only about a benefit and completely ignores that drugs have harms, which are much more certain to occur than their possible benefits.

 Fifth, if benefits and harms are combined in a preference measure, it is not likely that an NNT can be calculated because psychiatric drugs produce more harm than good. In this case, we can only calculate the number needed to harm (NNH). Drop-outs during trials of depression pills illustrate this. Since 12% more patients drop out on drug than on placebo,114 the NNH is 1/0.12, or 8.

 The UK silverbacks did not take any of these flaws into account when they claimed that depression pills have an impressive effect on recurrence, with an NNT of around three to prevent one recurrence.182 It is not surprising that patients want to come back on the drug when their psychiatrists have thrown them into the hell of acute withdrawal by suddenly substituting their drug with placebo. As only two patients are needed to get one with withdrawal symptoms,57 there cannot exist an NNT to prevent recurrence, only an NNH to harm, which is two.

 There cannot exist either an NNT in other depression trials, as the difference between drug and placebo in flawed trials is about 10%,4 or an NNT of 10, which is far less than the NNH. For example, the NNH for creating sexual problems is less than two for depression pills. Similar arguments and examples can be produced for all psychiatric drugs. Thus, the NNT in psychiatry is bogus. It doesn’t exist.

Possible answers to these problems lie with medical journals who should insist on the data from Drug Trials being published perhaps in conjunction with Treatment Trials and should not publish Treatment Trials without full access to their data. Our hierarchies of evidence should come clean on whether they regard a ghostwritten article without access to clinical trial data as better than or inferior to a Case Report that embodies dose responsiveness and CDR ?? elements for instance. And those deploying an analytic process should clarify how the resulting figures translate into the real world, rather than assuming they do.

But these problems avail of and aggravate a pre-existing epistemological gap rather than constitute the gap.

**Coda**

Evaluating the effects of drugs is among the most important exercises we undertake. When drugs work, they can like parachutes save lives. Well, they are the third leading cause of death, so this is what they do: they kill. Given the importance of the task, the notion of a hierarchy of evidence at the top of which are mechanisms that do the deciding for us has a potent allure.

Relegating judgement to the bottom of the evidence hierarchy in medicine brings out our discomfort with judgement – both clinical and pharmaceutical. The proliferation of Intention to Treat don’t introduce new concepts so late and with no further discussion and related analyses hinge on the same discomfort. Succumbing to an operational solution, however, is at least as dangerous as depending on judgement. You cannot make such a sweeping statement

In the case of airplanes, adding parachutes and other interventions that are effective (rather than just have an effect) enhances safety, although recent Boeing plane crashes point to the perils of too great a reliance on automatic decision tools. Please drop this. Airlines are very safe, much safer than any other means of transport

RCTs have led many to view drugs as being effective and safe, which is impossible. Some people will be harmed and some fatally. I don’t know anyone. Where are they? As a result, by the age of 50, close to 50% of us are now on five or more drugs. For the past five years, our life expectancies have been falling and admissions to hospital for treatment-induced morbidity are rising, an outcome that contrasts with the added safety of having parachutes and other gadgets in planes (Healy 2020). Current data indicates that stripping out the number of gadgets?? Drugs? from 10 or more to 5 or less reduces hospitalization, increases life expectancy and improves quality of life (Garfinkel and Mangin 2010).

While simply combining five pluripotent drug gadgets almost certainly brings risks of interactions that airplane gadgets don’t bring, if current RCTs of medicines essentially produce evidence that it is not correct to say this drug has no possible benefit, it makes sense to think that being on five or more drugs, of which all we can say in the case of each of them is that it is not right to say they have no possible benefit, might be a contributing factor to increasing levels of mortality and morbidity.

Recent data on life expectancies and treatment linked morbidities call for an evaluation of the role of RCTs in the evaluation of drug treatments (Healy 2020).

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