

**Review of Scientific Self-experimentation: ethics history, regulation, scenarios, and views among ethics committees and prominent scientists.**

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**Abstract**

We examined self-experimentation ethics history, regulations, use scenarios in universities and industry, along with attitudes. We conducted two surveys, first of ethics committees regarding policy and necessity of review for self-experimenting investigators. Second, we surveyed 16 types of self-experimentation among scientists in the National Academy of Sciences, the Royal Society, and the European Academy of Sciences.

We address misconceptions regarding self-experiments and examine historical context from the Hippocratic oath and Nuremberg codes, through the Helsinki Declaration and current Good Clinical Practices. Self-experimentation is approved of by Nuremberg code 5, the Helsinki Declaration references Nuremberg, and when the self-experimenter is a true investigator, there is no other person to be protected from unethical behavior. However, institutions are free to set their own requirements above and beyond this.

We cover real-world scenarios of self-experimentation: At universities; independent single-subject investigator at startup company; investigator participating in their own trial; investigator/employee at a large pharmaceutical firm; investigator/employee at a pharmaceutical firm using a drug to treat their own illness, and non-scientist self-experimenters brought into a later study. One law in the United Kingdom was found that may create a double-bind liability for universities and companies should something happen to a self-experimenting scientist affiliate.

Survey results:

Approximately 1/3<sup>rd</sup> of all ethics committee respondents had a formal policy, and 1/3<sup>rd</sup> did not require ethics review. Committees that handled significant numbers of self-experimenters are rare.

Half of prominent scientist respondents performed some kind of self-experiment, and roughly 1/5<sup>th</sup> of scientists had conducted a non-trivial self-experiment. Of those who conducted self-experiments, the mean was approximately 2 experiments with a range from 1 to 11 or more. Most scientist responders thought self-experiments overall were valuable, however, the fraction opposing them rose with perceived risk. Injection of biologics, exposure to radiation or radionuclides and surgical implants had negative ratings greater than positive ratings.

We examined the history of self-experimentation, finding in literature a 1.72% mortality rate, with no fatalities since 1928. Out of 14 Nobel prizes to self-experimenters, 7 self-experimented in the area of their prize.

**Introduction**

Self-experiments are controversial, for three reasons. Firstly, there is a widespread belief that a single experiment (an “N=1 trial”) in the life sciences is worthless, and that tests on multiple people (or animals) are required for *any* valid result. In this viewpoint, self-experimenters are at best putting themselves needlessly at risk, at worse generating misleading data in the process. Secondly, there is also a widespread belief that self-experimentation violates ethical norms for medical research. Lastly, there is a view that self-experimenters are putting themselves irrationally at risk – they should be protected from themselves. In this paper we argue that none of these viewpoints is valid, based on current evidence, ethics and the law.

*Table 1- Nobel prizes of self-experimenters*

<b>Recipient</b>	<b>Year</b>	<b>Prize</b>	<b>Self-experiment</b>
<i>Neils Finsen</i>	1903	<i>Phototherapy</i>	<i>Tested effects of sunlight and fractions of sunlight.</i>
William Ramsay	1904	Discovery of inert elements	Tested anesthetic effect of gases to find new ones.
Elie Mechnikoff	1908	Phagocytes	Injected himself with Borellia to help find cause of relapsing fever.
Frederick Banting	1923	Insulin	Gave himself mustard gas burns to test treatment.
<i>Charles Nicolle</i>	1928	<i>Cause of Typhus</i>	<i>Exposed himself to typhus to prove Koch’s postulates.</i>
<i>Karl Landsteiner</i>	1930	<i>Blood types</i>	<i>Tested his own blood for blood type research.</i>
Gerhard Domagk	1939	Sulfa drugs	Injected himself with sterilized human cancers
Ernest Lawrence	1939	Cyclotron	Drank water with radioactive sodium to examine sodium circulation.
George de Hevesy	1943	Polarography	Drank heavy water to determine half-life of H2O in the body.
<i>Max Theiler</i>	1951	<i>Yellow Fever</i>	<i>Tested yellow fever vaccine</i>
Albert Schweitzer	1952	Humanitarianism	Tested yellow fever vaccine
<i>Werner Forssman</i>	1956	<i>Cardiac catheterization</i>	<i>Cardiac catheterized himself to show it could be done safely.</i>
<i>Rosalyn Yalow</i>	1977	<i>ACTH</i>	<i>Tested her own blood in her ACTH research</i>
<i>Barry Marshall</i>	2005	<i>Helicobacter pylori &amp; ulcers</i>	<i>Drank a culture of H. pylori</i>

*Lines in italics* experimented in the area for which they won a Nobel Prize. Citations: [1-4]

Self-experimentation has a long and noble history that has led to many discoveries, eight of which have been worthy of a Nobel Prize. Werner Forssmann shared the Nobel Prize in 1956 for his catheterization procedure that he did on himself with the assistance of a nurse [5]. Max Theiler received the Nobel prize in Medicine in 1951 for his contributions to yellow fever and was first to test his vaccine [1]. Barry Marshall shared the 2005 Nobel Prize in Medicine for discovery of the connection between Helicobacter pylori and gastric ulcers [3].

The history of scientific testing, where the primary or lead investigator used themselves as a research subject, goes back centuries. Wiese documented 465 cases of scientific self-experimentation up to 2003, and 13 Nobel Prizes going to self-experimenting

scientists up to 1999 [2]. He noted 8 deaths from self-experiments. Wiese used two books as his data source, the second published in 2003[1, 6]. He missed Max Theiler's 1951 Nobel Prize, Barry Marshall's 2005 Nobel came after, and we removed Victor Hess' from the self-experimenter Nobel prizes that Wiese counted which gives us 14 Nobel prizes that went to scientists that conducted experiments on themselves.

Based on Weisse' sources, since 1975 there have been at least 40 self-experiments by scientists. We believe that there are probably many times that number[7].

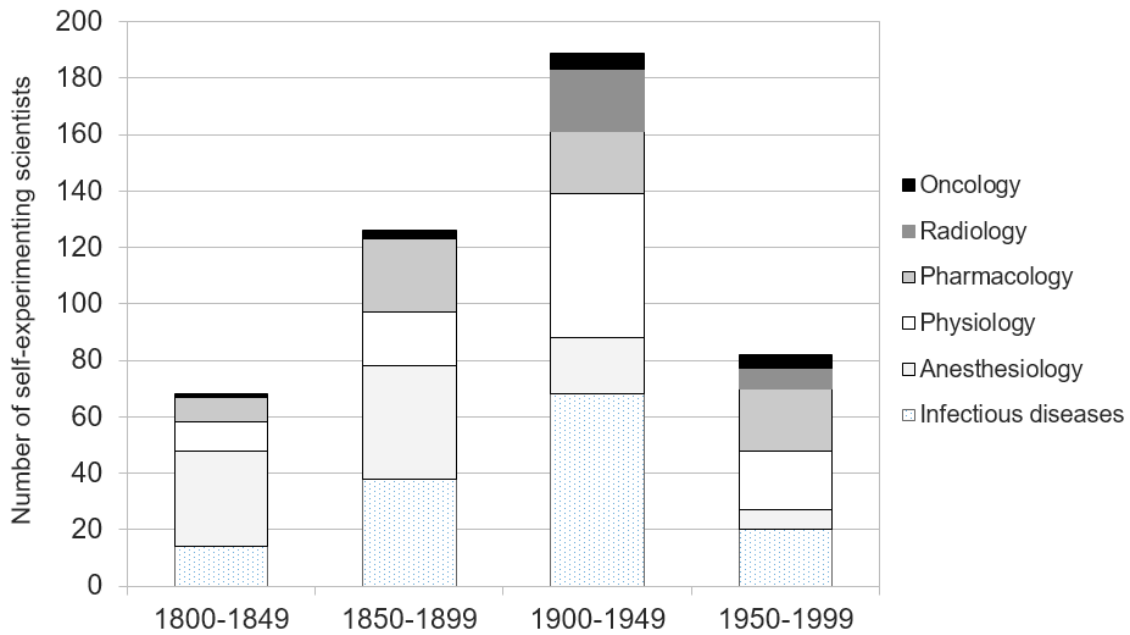


Figure 1 - Documented self-experiments 1800-1999.

Self-experimentation continues to be carried out in the 21<sup>st</sup> century. In 2014, Philip Kennedy had electrodes implanted into his speech center to further his research on direct brain interfaces [8]. In 2016, Alex Zhavoronkov self tested drugs which his software algorithms identified as likely candidates [9].

### Ethics regulation in medicine

There is no law nor regulation identified that requires investigators experimenting on themselves to consult an ethics committee. To the extent that ethics committees require this, it is institutional choice.

#### *Hippocratic Oath*

Hippocratic Oath from ancient Greece is the oldest ethical foundation of medicine[10]. Most physicians no longer swear the oath to, “Apollo, Physician,

Asclepius, Hygieia, Panacea and all the gods and goddesses.” Certain parts are considered today to be not always in the best interest of the patient, anachronistic, or matters of contention. Surgery has been absorbed into medicine, and is no longer separate from it. Women can be trained as physicians today, and students pay for their medical education. Physicians may perform abortions in some jurisdictions, or the rules may vary. Euthanasia is considered acceptable by some physicians under proper circumstances, and is legal in some jurisdictions.

Core Hippocratic principles are retained: to do no harm; to put the interests of the patient first; to not commit injustice toward patients; to not engage in sex with patients under care, (whether slaves or free folk); and to keep all patient matters strictly confidential. Considering the sexual mores of ancient Greece visible in literature of the time, that Hippocrates forbid physicians to make sexual advances on patients, and specifically forbid doing so with slaves under care, is notable.

#### *Pre-Nuremberg Ethics*

A 246 page book by Thomas Percival published in 1803 lays out responsibilities for physicians and surgeons[11]. This book covers conduct with patients, colleagues, and pharmacists in great detail. Percival’s text was adopted by the Royal College of Physicians and republished in 1847. It was adopted by the American Medical Association in 1849[12]. Percival’s excellent book has, however, been superseded by the codes of ethics laid down at the Nuremberg Trials that followed from the atrocities of WW-II. In addition, Germany and Russia both had laws regarding medical ethics in experimentation in the first half of the 20<sup>th</sup> century[13]. This shows that ethics is not just a matter of law or regulation, it requires a culture of adherence to practice.

#### *Nuremberg Principles*

***5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur, except, perhaps, in those experiments where the experimental physicians also serve as subjects.***

*- Nuremberg court, principles of human experimentation [14]*

The formalization of modern ethical practice in biomedicine is rooted in a series of outrages that occurred in the 20<sup>th</sup> century wherein people were used as test subjects and suffered terrible consequences, either against their will or unwittingly. The Nazi experiments conducted on prisoners in concentration camps led to war crimes trials. Those trials in 1945-46 used the Hippocratic Oath and other precedents as a basis to formulate the Nuremberg principles of 1947 for protection of medical research subjects[14]. The Nuremberg principles are the foundation of modern medical ethics.

The object of the Nuremberg principles is to make explicit the Hippocratic principle that the doctor should “do no harm”; medical practice should be for the benefit of the patient, and if for research that does not directly benefit the patient then should not harm the patient. It also required that the patient consent. Notably, article 5 of the Nuremberg principles states that high risk of death or disabling injury may be acceptable where the experimenters are also subjects of their experiments. This is the only known direct address to self-experimentation in medical ethics. Since article 5 covers the case where disabling injury or death could occur, by extension it also covers lesser risks to self.

#### *Declaration of Helsinki*

The 1964 Declaration of Helsinki was the first major public effort by medical scientists to codify the responsibilities of medical experimenters [15]. The Helsinki Declaration eased the requirements for consent, changing it from Nuremberg's declaration that consent was “absolutely essential” to “if at all possible”, and allowing proxy consent from a legal guardian. The 2008 version of the Helsinki Declaration includes the word ‘consent’ 20 times and the 2013 version 27, but both versions only include the word ‘self’ once, in the context of the right of patients to self-determination[15, 16]. Article 14 of the Helsinki Declaration defined that a clinical protocol should be a written document, kept up to date with revisions that are approved by a review committee, and inform subjects of conflict of interest and risk. Helsinki's guidelines remained voluntary for 10 years in the United States. The Helsinki Declaration is the basis for ethics committee review.

The Belmont Report of 1979 on human subjects, based on the Helsinki Declaration, laid out “respect for persons, beneficence and justice,” and informed consent without coercion, as the guiding principles of ethics committees [17].

In much of Europe, the review function is held by the Institutional Ethics Committee (IEC) which is also known by various other names. Netherlands uses Medical Research Ethics Committee (MREC), Sweden the Ethical Vetting Board (Etikprövningsnämnden), France the Comités de Protection des Personnes (CPP), Canada the Research Ethics Board (REB), Australia the Human Research Ethics Committee (HREC), a Research Ethics Committee (REC) is the name in Italy, Spain, Portugal, Germany, the UK and Ireland, and in Japan it is 倫理委員会, or, in English, ethics committee. Countries may have their own common names as well. These are equivalent to the Institutional Review Board (IRB) in the United States, constituted to fulfill the purpose laid out in the Helsinki Declaration.

#### *Public law on research ethics committees*

In 1972, Peter Buxtun, a former employee of the United States Public Health Service, went public, revealing that he had complained about the unethical treatment

of subjects in the Tuskegee study since 1966 [18]. This led to the passing of public law 93-348 in the United States in 1974, which included the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [19]. This required ethics approval before conducting any human experiments with federal money or before conducting any clinical trials, whether public or private. Other countries followed over a few decades. Germany formalized this requirement in 1994[20]. The first formal ethics committee in Japan was established in 1982, but regulations requiring it for clinical trials did not appear until 2003[21].

Tuskegee was not the only study of its kind. In 2010, a study conducted by the US Public Health Service (PHS) and the Pan American Health Organization came to light that had deliberately infected Guatemalans with sexually transmitted diseases such as syphilis and gonorrhea from 1946-1948[22]. Similarly the crimes prosecuted at the Nuremburg court are not the only cases of war time medical experiments on prisoners. Imperial Japan conducted such experiments as well[23].

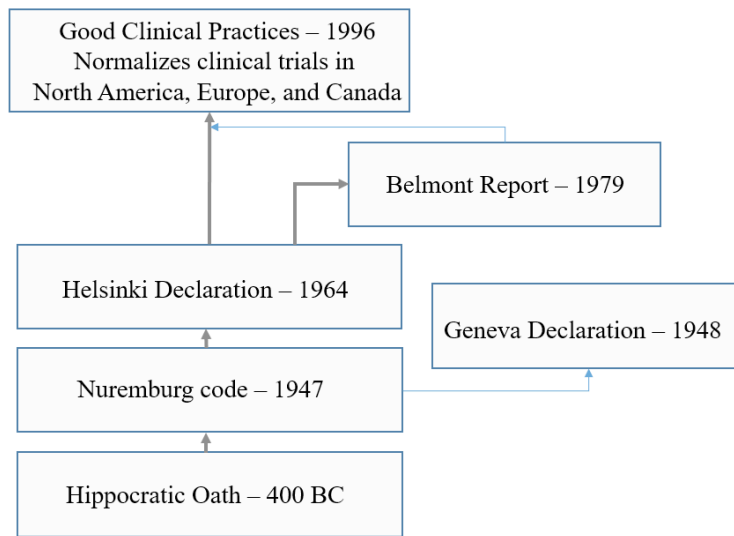


Figure 2 - Clinical trial ethics documents precedence tree.

*Good Clinical Practices – worldwide normalization of practices*

*2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s). ICH GCP (R1 & R2).[24, 25]*

Since the Belmont Report, in late 2008 in the USA, the FDA modified regulations so they no longer refer to the Helsinki documents, and instead refer to Good Clinical Practices(GCP) [26]. GCP is a broader set of requirements that includes regulations on a

wide range of aspects of clinical research conduct, including such matters as traceability of methods and materials, data collection and handling, and trial reporting, all aimed at ensuring that clinical experiments generate valid data while minimizing risk to patients. GCP is principally aimed at clinical tests of new drugs, devices or procedures, but also applies to ‘pure’ experimentation. GCP is a product of the International Conference on Harmonization (ICH) of 1996 and 2015 that aligns clinical trials in the US, Canada, Australia, Europe and Japan. Other countries are working toward inclusion in this harmonization, including Russia, Ukraine, Eastern Europe, and Central Asia[27], China[28], and India[29]. There is sometimes a misapprehension that GCP has jettisoned Helsinki, however, ‘*Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance*’ of 1996, for release 1 (R1), and the 2015 draft release 2 (R2), are built on Helsinki, as stated by reference in the introduction, section 2.1, and section 4.81[24, 25]. Helsinki, in turn, references Nuremberg. However, not all jurisdictions accept all versions of the Helsinki document, which is why we cite both the 2008 and 2013 versions.

GCP requires external review of protocols to ensure that the interests of the patient/subject are protected. This is the role of the ethics committee. In the USA such review is carried out by the Institutional Review Board (IRB).

In January of 2017, the USA’s FDA published modifications to exempt certain low-risk studies from IRB review, and make other low-risk study IRB reviews limited to privacy [30]. These exemptions take effect in 2018.

In summary, the primary purpose of an ethics committee review is to protect potential research subjects from investigators and bureaucracy that acts without conscience, or who are implementing a dangerous protocol without proper consideration. Secondly, an ethics committee review is present to ensure that subjects obtain benefit and are protected from undue pressure. In addition to the review function, the ethics committee review has also become a de facto institutional record of experimental protocols which may be valuable for historians.

There is no ethics statement, law nor regulation identified in any territory that we have explored that requires investigators experimenting on themselves to consult an ethics committee. To the extent that ethics committees require this, it is institutional choice.

#### *Other forms of legal responsibility*

In the United Kingdom the “Corporate Manslaughter and Corporate Homicide Act of 2007,” appears to be able to hold an organization responsible in the case of a death of a self-experimenter, since universities and the NHS are ‘Crown bodies,’ (servants or agents of the Crown) and hence to be treated as any other corporation[31]. The law additionally allows for simultaneous prosecution under the Health and Safety legislation. This Corporate manslaughter law holds an organization responsible in the case of a death of someone for whom they have a “Duty of Care”.

Several questions are unanswered, since this is a new law. First, does this law apply to a self-experimenting scientist, or would the existing health and safety law take precedence? If the corporate manslaughter law applies, then, what is the duty of care relative to self-experimenting scientists in their employ? Is it a gross negligence standard, or will it hold an institution to a more paternal duty of care? Since scientists are rather close to defining the proverbial “herd of cats,” this could prove vexing to university and hospital managements.

As one lawyer informally commented on the UK law, in event of a death, “In front of rows of widows and orphans, the University will have to explain to the court how this death occurred if this experiment was so safe - and indeed what steps they took to satisfy themselves that it was safe.” The law is extremely vague on what evidence can be used to provide such proof. UK institutions may be understandably concerned about the idea that an employee’s activities could open them to such prosecution, regardless of the actual risk.

Against this, it must be noted that deaths and harm do occur during clinical trials and human experiments. A major practical purpose for requiring ethics committee approval and regulatory permission to conduct clinical trials is that this conformance protects the parties from prosecution unless the agreed procedure of the trial has been seriously violated. Since all human experiments have potential for death, and a self-experiment is just another case of human experimentation, it would make sense that if there is an ethics review approval, this should cover a self-experiment just as it covers any other human experiment.

The UK is unique at present in the scope of its law. Ireland introduced a corporate manslaughter bill in 2016 containing a gross negligence standard, which failed to pass [32]. New Zealand introduced a similar law in 2015, which also failed to pass [33]. Canada passed a corporate manslaughter bill in 2004 that requires employers to take reasonable steps to prevent bodily harm arising from that work or task, as well as liability for negligence [34]. In the USA, personal injury law also imposes a duty of care on employers, however, there is no evidence this has been, or would be used against an institution in the case of the death of a self-experimenting scientist. Legal precedent sets a fairly high standard for negligence.

#### *Open questions in ethics review*

We found no figures or data on the effectiveness of ethics review, and others have called for research into how well ethics review is doing its job. The questions raised by Coleman and Bouësseau remain unanswered [35]. To what degree does ethics review improve: understanding of risks and benefits; subject decisions to participate; subject experiences in studies; reduction in risk; responsiveness to the community's needs; and how well researchers follow documentation? All we have is anecdotes and institutional lore. However, history does suggest, that at least in the USA, ethics review has prevented the most egregious abuses of subjects from recurring.



We also do not have information on the cost of ethics review to investigators, only anecdotes that sometimes the costs are quite steep, which may make a self-experimenting investigator choose not to seek review when cost is a concern.

### Rejection of self-experiment manuscripts without ethics review.

Article 30 of the Helsinki Declaration of 2008 (36 in the 2013 version) directs that journals not publish what does not adhere to Helsinki's requirements and most journals implement this, although some will extend waivers. However, since Helsinki is based on the premise that the experimenter and the subject are different parties, we do not think that article 30 of Helsinki applies to self-experimenters. As already noted, article 5 of the Nuremberg principles is the only explicit mention of self-experimentation and approves of it as an ethically positive choice. In addition, when the subject and the investigator are the same person, what basis is there to intervene between them?

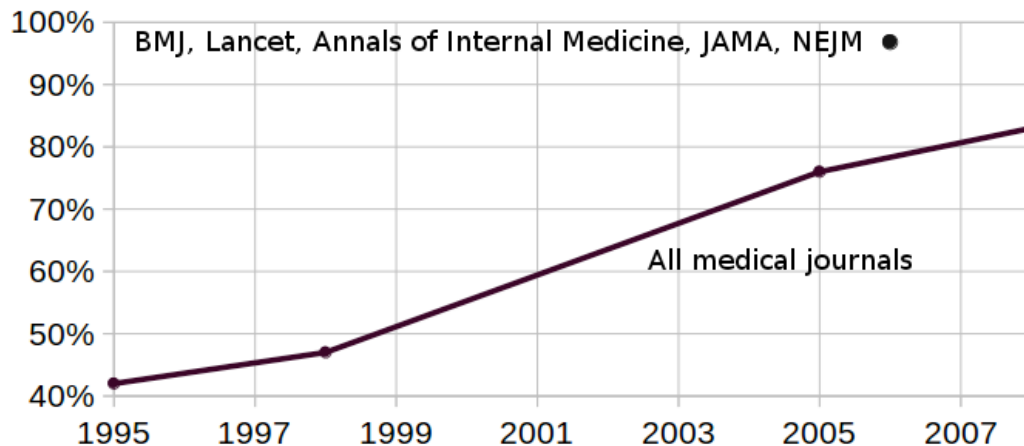


Figure 3 – Published papers conformance to Helsinki article 30 requirement for ethics review[36-38]

We found an instance of a manuscript that was rejected, in part, because it was a self-experiment without oversight from an ethics committee. The author appealed this ruling to the Committee on Publication Ethics (COPE)[39]. COPE upheld the journal's right to reject the manuscript in accordance with its guidelines, which guidelines required ethics committee approval for all human subjects[40]. However, no concern was expressed in this rejection about the ethics of self-experimentation, per se. This author later published two papers from his observations in another journal.

### Self-experimenter views and motives

We conducted discussions with self-experimenting scientists, and reviewed literature on self-experimenting scientists. We identified five classes of reasons for self-experimentation:

1. *Learning what subjects to a protocol would experience, and noticing effects that might be missed when operating through the relative distance of others.* A research protocol, while it is intended to protect human subjects, is also a straitjacket that makes it cumbersome, or impractical, to examine new areas that might show up. Consequently, taking on the role of the first subject in a study can allow the scientist more flexibility in the early stage of an investigation.
2. *Providing an initial test to confirm that research performed in animals can be translated to humans.* This would typically be a ‘spot check’ that a pattern of effects (for example markers) from a drug affecting a pathway that is seen in an animal model was also seen in humans.
3. *Avoidance of the considerable amount of time, expense, and red tape of conducting experiments on others by conducting a self-experiment[9].*
4. *To pilot on one person an experimental procedure that would be impractically resource intensive or expensive if performed on many people[41, 42].*
5. *Proving that something is safe/true when no-one else will believe you.*

### **Survey of ethics committees regarding investigators as self-subjects**

Because ethics committees have a key role in regulating human experimentation, and as self-experimentation is by definition human experimentation, we explored ethics committees’ views on it. Ethics offices at 203 universities or national health services were queried by email regarding policy on investigators as self-subjects, and if they required ethics committee approval for such.

We had 47 responses, 11 of which did not answer the questions. Interestingly, 8 of those 11 came from the UK, where fully half of all responders had mastered the fine art of fielding the question without answering.

24 of the 47 ethics committees had a policy on self-experimenters and 12 did not, however, there was no correlation between having a policy or not and requiring an ethics review. 25 ethics committees said they would require an ethics review for a self-experimenter. 12 ethics committees said they would not require it.

Two ethics committees justified review on the grounds that it was the ethics committee's job to protect over-enthusiastic investigators from harming themselves. One of those indicated that they would designate a surrogate investigator to obtain written informed consent from the primary investigator, if the protocol was thought risky enough. One research office considered single-subject experiments to be not meaningful due to an *N* of one.

The most common position of the roughly one-third of research offices that did not require ethics committee approval for a self-subject investigator was that the ethics

committee's purpose is to protect subjects from potential abuse and harm by investigators. When those are the same person, there is no justification for intervening. Even when ethics committee approval was not required, however, some encouraged investigators to submit notification to the ethics committee. A number of responders noted that there was no regulation and no guidance on self-experimentation. This is not quite correct, as the Helsinki Declaration is founded on the Nuremburg principles, of which number 5 speaks to self-experimentation. However, this view is certainly understandable.

Two responders indicated familiarity with self-experimenters at significant numbers, both of them top universities. One did not require an ethics review and said that the primary concern is whether or not it would really be a self-experiment, and not a disguised small group experiment. That committee would have informal discussions and educate experimenters regarding possible violations of the law in their jurisdiction. The other university that was familiar with self-experimenters was the one mentioned above that might assign a surrogate to obtain informed consent if the procedure was deemed risky enough.

### **Self-experiment survey of prominent scientists**

A total of 1072 members of the National Academy of Sciences, the Royal Society, and the European Academy of Sciences were sent an online survey by email. Over 3 months, 52 surveys answered the question on types of self-experiments they had done, but only 32 answered on the value of these experiments. Out of the 52 respondents, 26 did not conduct self-experiments and 26 did. All 26 self-experimenters filled out the question on the number of times they had self-experimented. Of these 26 self-experimenters, 6 got ethics committee approval for an experiment. Of these 26 self-experimenters, 10 of them performed self-experiments of types 5-16 as shown in figure 3 (“5. Tissue biopsy” to “16. Other”). If venous blood draw (type 4) is included, then the number goes to 19.

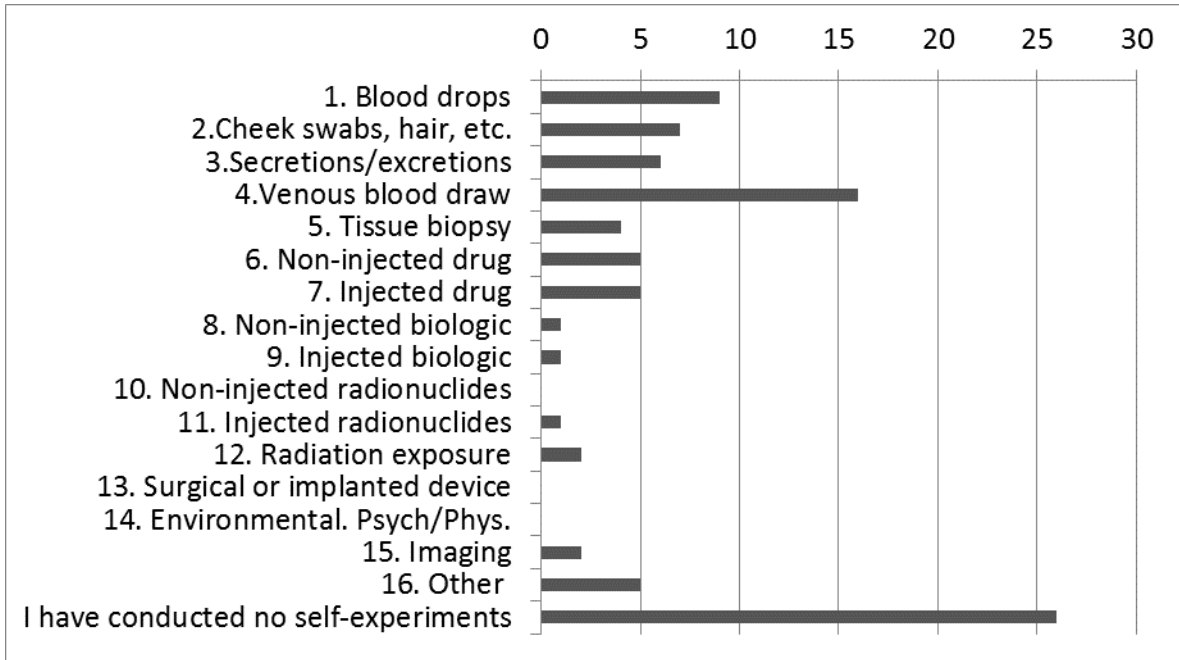


Figure 4 – Respondents who performed various types of self experiments. Multiple types of self experiments could be performed by one scientist. There are many types of self-experiments, and our list is not exhaustive.

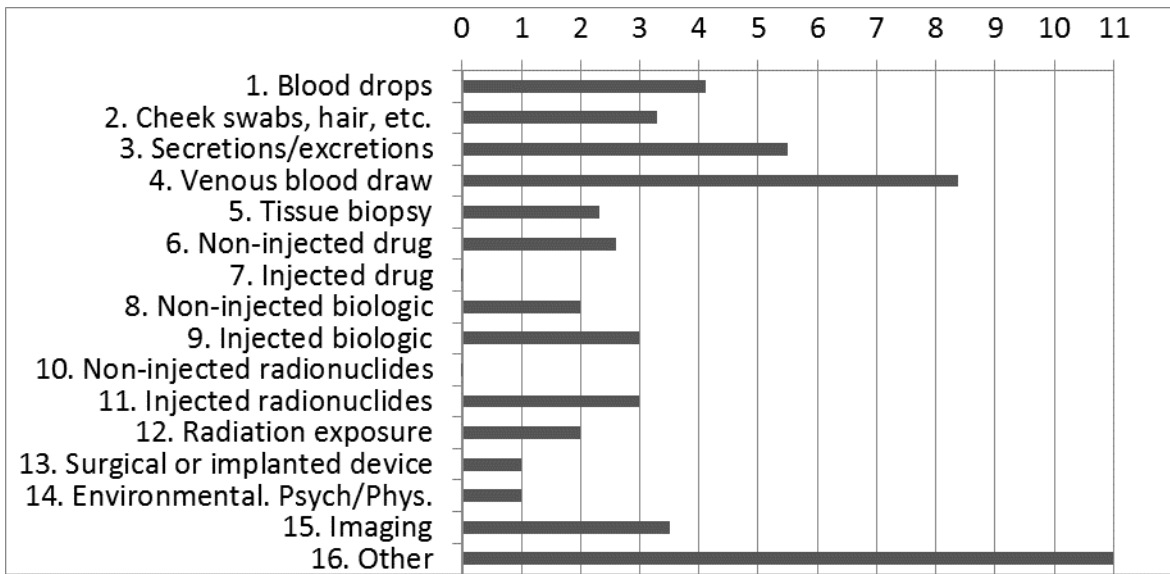


Figure 5 - Average (mean) number of times that scientists who experimented on themselves reported conducting each type of experiment.

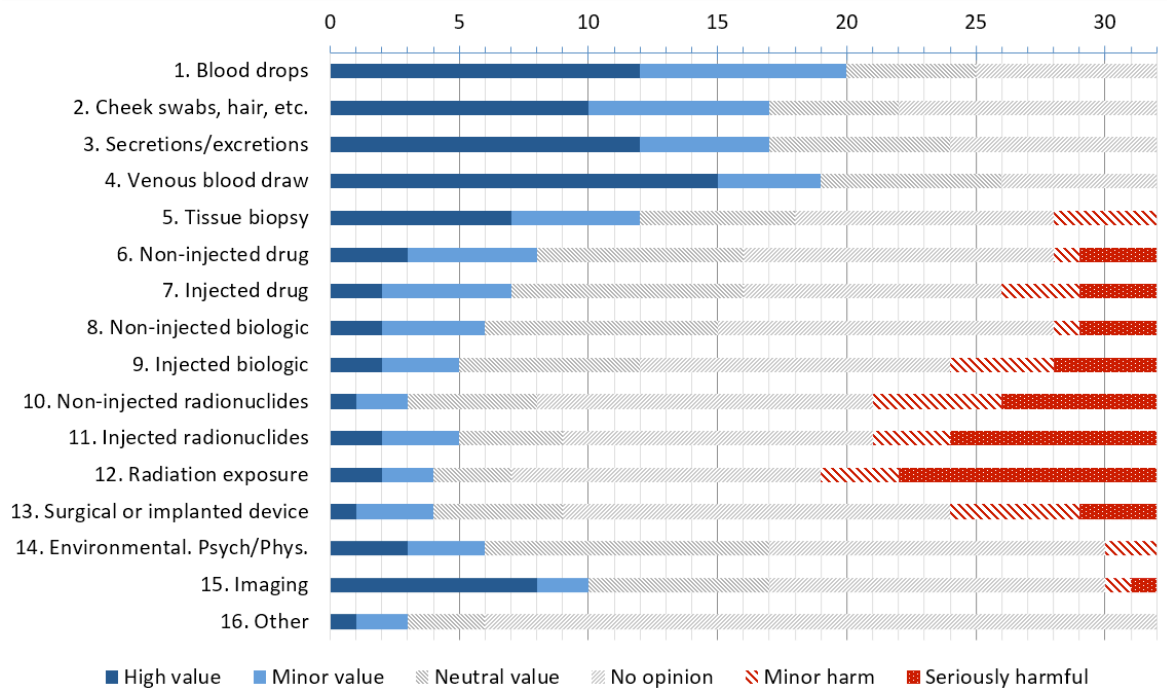


Figure 6 – Perceived value to science of each type of self-experiment.

Our sample of prominent scientists appears fairly engaged in self-experimentation. For this group of active responders, we considered that selecting no opinion is equivalent to expressing a neutral opinion on the value of self-experiments. High intervention non-radiological experiments (categories 5 through 8 and 14 through 15 in Figures 6 through 8) are considered hazardous (i.e. of questionable risk:reward benefit) by a significant minority of respondents. Injected biologic, surgical, and experiments involving radiation exposure are considered overly hazardous self-experiments by more respondents than considered them beneficial. (We note that categories 10 through 12 above include imaging studies, and in all cases, the dose of radiation should generally be quite low.)

Is this support for self-experimentation by our sample justified? This must depend on the risk:benefit ratio, which itself brings up the question of whether the experimenter themselves can objectively evaluate the risk:benefit ratio.

### Risk of self-experimentation

The ethical right of scientists to expose themselves to those risks appears clear as long as they are competent investigators, as was codified by article five of the Nuremberg principles. But what are the actual risks?

#### *Risk of death in self-experiments*

Table 2 - Deaths of self-experimenting scientists.

Scientist	Year	Cause of death
Alois Rosenfeld	1817	Bubonic plague
Anthony White	1849	Plague
Otto Obermeier	1873	Cholera vaccine
Joseph von Lindwurm	1874	Secondary syphilis
Daniel Carrion	1885	Bartonellosis
Jesse Lazear	1900	Yellow fever
Arthur Bacot	1920	Typhus
Alexander Bogdanov	1928	Incompatible blood transfusion

Risk of death from self-experiments does not appear likely in the present era. Weisse recorded 8 (1.72%) deaths out of his 465 self-experiments in 203 years. This historic mortality rate may be comparable to the approximate 1% acute mortality rate in orthopedic surgery[43]. However, all but one death was from self-inoculation with an infectious disease, and 5 of these occurred in the 19<sup>th</sup> century when the germ theory of disease was being investigated. The last self-experiment death was Alexander Bogdanov in 1928, from transfusion with an incompatible blood type. Since that time, there have been at least 190 self-experiments documented in literature, without a single death( Fig.8)[1, 2].

*Risk of non-fatal self-harm*

We could not find statistically sufficient data on rates of significant non-fatal harm from self-experiments. However, there are cautionary cases. John Stapp, an American career U.S. Air Force officer, physician, and pioneer in studying the effects of acceleration and deceleration forces on humans, acquired permanent vision problems in 1954 after sustaining his last deceleration of 46.2 G[44]. He did not do any more deceleration experiments on himself after this. Prior to ending his acceleration self-experiments, Stapp suffered broken bones and concussion. Philip Kennedy's 2014 first operation to implant electrodes into his speech center caused him to lose the ability to speak, but he did recover[8]. Nikola Tesla experienced burns to his eyes and skin from x-ray exposure[45].

These few incidents indicate that there is a case to be made for urging scientists planning self-experiments to be careful and submit their experimental plans for external review. However, the data is sparse, and unrecognized risk of self-harm does not appear to be a serious problem.

*Risk discussion*

Self-harm (as well as death) could come from risks taken for one of three reasons.

- I. The risk could be known, acknowledged, and accepted. As noted above, the scientist understands the risk, but considers it unethical to expose someone else to risks they are not willing to take themselves. John Stapp was certainly well aware

of the risk he took, and accepted it. Philip Kennedy, the inventor of the neurotrophic electrode, also knew the risks.

- II. The risk could be known by those knowledgeable in the field, but not by the experimenter. We do not have any examples of this. Self-experimenters seem to be motivated to find out everything they can about an experiment before trying it (a point we return to below).
- III. The risk could be unknown to anyone at the time. Nikola Tesla didn't know the dangers of high doses of x-rays, nor did Marie Curie understand the dangers of radiation. Together with many others in the early days of exploration of imaging using high energy radiation, they paid for their curiosity with injury[46].

In both death and self-harm, risk boils down to two issues. First, has the self-experimenter evaluated and understood the risks? This is possible in the first and second case, obviously it is not possible in the third case. Second, do they accept the risks?

The former is a reasonable cause to suggest oversight and review. The second is a fundamental ethical choice. That choice is on par with whether people should be allowed to go running with the bulls in Pamplona, base-jump, climb mountains, smoke tobacco, or drink alcohol. Wrapped in with this second ethical question is how much benefit there may be to the experimenter and others from the experiment.

### **Benefits and meaningfulness of self-experimentation**

*Case reports can have the following functions: (I) descriptions of new diseases; (II) study of mechanisms; (III) discovery of new therapies; (IV) recognition of side effects; and (V) education. - Yi-Xiang J. Wang (2014)*

The question of self-experimentation benefits is inextricable from the issue of whether such a “low statistical power” experiment has meaning. Self-experimentation is simply another single case report in medicine. Medicine is founded on case reports, collected and passed on from the time of the Ancient Egyptians, Hippocrates, and Galen[47, 48]. The clinical case report remains a major part of modern medical science[49, 50]. In the current century two notable single case reports are a recovery from rabies[51] and the Berlin patient HIV cure[52].

In some areas, such as cancer treatment, single cases aren't meaningful, regardless of the result. However, extending this issue to all of medicine requires assuming that there is no common anatomy, physiology, or biochemistry in the human body, and that diseases do not share common characteristics. These observations apply equally to both self-experiments and any other single-subject case report.

As Altman and Roberts discuss, self-experiments, even when conducted in the soft and complex fields of behavior and psychology, have usually been confirmed [1, 53]. Altman also concluded that scientists have little incentive to falsify results of self-

experiments. Such motives tend to appear farther down the line after commitment of resources.

In our examination of literature, only once was a self-experiment result shown to be false – an experiment by Max von Pettenkover in which he failed to become seriously ill with cholera after drinking a culture of *Vibrio cholerae* and then taking bicarbonate of soda[1]. It is possible that the culture he drank was missing the CTX $\phi$  bacteriophage that codes for the required toxin, or that Dr. Pettenkover had acquired sufficient immunity previously.

We believe there are other self-experiments which had results that would not stand up to an expanded study. One possible reason why this could be is that scientists did further experiments to verify their result, and if it did not hold up, would be unlikely to publish. This bias is recognized in case report literature. However, given the extensive literature available, this is not sufficient reason to claim that it is a terribly serious problem.

Experiments can be designed so that third parties make measurements or perform assays to eliminate bench error bias. By having third parties take samples, and confirm identity, self-experimenters can avoid questions of credibility and veracity as well. We recommend that self-experimenting researchers do this when it is practical.

We are also finding out more about how individual humans differ, and single, or self-experiments can shed light on this. Large trials tend to smooth those differences out. An  $N=1$  trial removes that source of variation, especially if it is a swap-over trial design where the same person switches between treatments/diets/tests. Michael Snyder's massively parallel self-analysis experiment, the Snyderome, is an example of this[41, 42]. He detected changes in his state that were within the 'normal' range as defined by population distributions, but were nevertheless highly significant. Thus  $N = 1$  experiments can also give a different *type* of information.

There is support within medicine and science for moving research ahead and also for the idea that the value to the many outweighs discomfort or risk for one as expressed by Wiese, and others[1, 2]. There is also support for the idea that physicians and scientists may test on themselves to further their own knowledge, as Rebecca Dresser and Oliver Sacks have discussed [54, 55]. And, it may be impossible to know the value of a piece of research until after it has been performed (sometimes decades after).

Lastly, single subject trials can provide a 'spot check' that results found from animals might be translatable to humans. If animal experiments provide a robust pattern of information, for example, a relationship between biomarkers and physiological state, then the hypothesis that this is mirrored in humans can be tested (although not proven) with a single test. Given the reproducibility crisis in biomedical science, such validation of animal observations in human subjects provides a valuable step from lab work to full-scale clinical or field trial. Thus, we conclude that while single-subject experimental results may need validation in a larger population, they can obtain meaningful results that are quite important.



### **Investigator self-experimenter scenario discussions**

We present scenarios drawn from real world cases where scientists have been involved in self-experimentation to stimulate discussion, and describe our views.

#### *Independent single-subject investigator*

An independent investigator experimenting on themselves has no legal or ethical obligation to consult an ethics committee. However, we think it is a service that should be easily available on a voluntary basis both to provide review and to make it easier to publish results for the investigator. There may be merit to codifying this as a streamlined type of ethical review that only seeks to ensure the investigator is aware of risks.

#### *Investigator participating in an ethics committee approved study at a small or startup company*

Similar to an independent investigator, a startup founder self-experimenter has no requirement to consult an ethics committee. If founder investigators in small companies get ethics committee approval and make themselves a subject of an ethics committee approved protocol, there is neither regulation nor moral imperative that obligates them to tell the ethics committee that they will be a subject unless that ethics committee chooses to ask. Whether an ethics committee cares to know is a matter of the ethics committee's choice. In this case, an ethics committee and regulatory approval is required for any subject other than the investigator(s).

#### *Investigator working at large pharmaceutical firm*

Whether a scientist at a large pharmaceutical company makes themselves a subject on an ethics committee approved protocol may be a matter of company policy. There are multiple possible scenarios in this case.

First, an investigator on a project may try an experiment in the lab without approval or consulting anyone, often, based on an accident. Historically, this is fairly common. For instance, J.D. Searle was the chemist who discovered Aspartame by accidentally tasting a drug synthesis intermediate [56]. Albert Hoffman famously discovered LSD by accidentally ingesting it, and then deliberately dosing himself [57]. He also self-tested hydergine, which became a major drug for Sandoz. It would seem that companies that make policies that are overly restrictive may be hurting their long-term profitability by preventing potential discoveries or advances in science.

Second, an investigator may decide to make themselves part of their own protocol in a clinical trial. Obviously this depends on the investigator being a suitable subject. However, there is a reasonable argument that investigators could feel themselves under

pressure to do so from superiors or from peers. We have anecdotally heard this was the case in one major pharmaceutical company in the past, and that is corroborated by the publicly recorded accounts given above. We think companies should strive to strike a balance between preventing coercion, and allowing qualified scientists to be subjects in their experiments should they wish to be, and that an external review would be best.

*Investigator/employee of a pharmaceutical firm uses a drug to treat their own disease*

What about a scientist working as an investigator in a large pharmaceutical company who develops the disease that the investigational drug can treat, prior to approval for general use? A scientist could simply administer the drug to themselves without asking permission, which could be considered a kind of theft from the company, but could likely be overlooked. They could also ask the company for permission to use it, which would put them in the position of being a phase 2 or 3 subject of the clinical trial. If the company is still in phase 1 that might present issues for data analysis, and if the disease is serious enough, the investigator may not be willing to wait. Similarly, if the individual is treating themselves for condition B and the clinical trial is only aimed at condition A, this could also present problems for data analysis, depending on the design of the trial, and possibly for the company's patenting strategy.

If there is no clinical trial, then it would be a matter of compassionate provision of the materials on the part of the company. With "right to try" laws in a majority of states, and because people can administer what they want to themselves, this should be acceptable[58], although there are certainly concerns for those running a trial[59]. The most fundamental problem is that problematic data at the wrong stage can potentially destroy a potential new product, by requiring expansion of the study to numbers that are beyond the budget.

If the company denies permission, then we get into another area of law. The World Intellectual Property Organization (WIPO) finds that experimental and research use of an invention is legal in most countries[60]. In the United States, there is a common-law exception allowing de minimis experimental use that is strictly limited to an individual's personal interest without any intention to profit. This was enlarged by the Hatch-Waxman Act with amendment §271(e)(1) the "Safe Harbor Provision." [61]. This allows "uses reasonably related" to pursuing FDA approval, although it does not necessarily require that an FDA application be filed [62].

If the company denies permission, the simplest solution for the interested investigator-user of the drug is to synthesize it themselves. Often, this should be within their abilities. If not, then a contract chemistry company could make it.

Considering this case of an individual with a disease in light of these elements of law, the person would pass the narrowed de minimis experimental use common-law

exception as it would be personal interest and not for profit. They would also fall under the Safe Harbor Provision of §271(e)(1), as long as the use was recorded, with sufficient follow-up data collected that could be made available to regulators at some future date in order to fulfill the “reasonably related” clause.

*Non-scientist self-experimenters brought into a later study*

Non-scientists conduct experimental procedures on themselves, and some are quite knowledgeable and keep very good records of what they do. For instance, Bill Haast, Tim Friede, Harold Mierkey, and a number of others have pioneered immunization of themselves to venomous snakes, insects, arachnids, and fish [63]. Bringing such non-scientist self-experimenters into a study presents some significant issues for an ethics committee.

First of all, it is their protocols that have been implemented rather than the investigator's, and there may be some variation over time and between individuals.

Second, whether the experiments occur or not is not up to the investigator. Whether protocols given to the investigator were or will be followed or not is not under the investigator's control either. In this sense, it has similarity to studies of recreational drug users and addicts, however, the study group may understandably take umbrage at such a comparison. The records received in the study will generally be historical.

Third, because the investigator will not have control over administration, dose, or conditions, it will be impossible for the investigator to provide the safety assurances that ethics committees want.

Fourth, the investigator may be limited to following the group with blood work or questions and making suggestions to people who may well be ahead of the investigator in practical ways. This would require that the investigator have quite a bit of flexibility, which could entail regular updates to the protocol document in ways that do not fit the Helsinki paradigm.

Last, members of such a study have opinions of their own on how things should go, and expect benefits from the research. This latter is part of the Helsinki paradigm, however, what the benefits desired are may vary from subject to subject. This kind of study will require a more collaborative approach than is commonly the case. Precedents from studies of Native American communities have bearing, and the study could borrow some principles of community-based participatory research (CBPR) [64]. None of this would fit the usual templates for investigations.

Collecting data from non-scientist experimenters does not require an ethics committee, because these people designed and implemented their own experiments. However, they are not, at least formally, qualified investigators. Some of them petition strenuously to be studied and taken seriously by scientists, and this leans strongly in the direction of justifying non-requirement of an ethics committee. Some display excellent

competence. We think that an ethics committee should accept such study applications, and make allowances for flexibility as we have discussed. However, such studies do fall outside the Helsinki paradigm.

### **Concluding remarks**

History and moral authority of ethics allows for investigators to use themselves as experimental subjects. Similarly, the history of science shows that self-subject experiments by scientists are of significant and sometimes great value to society.

Scientists running studies should normally represent the definition of informed consent [67]. Qualified scientists who run experiments on themselves are distinct from family members, graduate students, staff, and others who may be subject to any significant level of coercion. There are instances when a graduate student, or staff member, might undertake a self-experiment without coercion. However, we are not clear how an institution can tell the difference, except for the occasional *fait accompli*, and further consideration of this could be helpful.

Ethics committee review is not required for self-experimenters, and we should not lose sight of the fact that history shows that scientists will perform self-experiments despite knowing that such an experiment would be disapproved of and suffering serious repercussions for doing so [65]. Thus, attempting ban self-experiments would be a self-defeating exercise that would probably do more harm than good. Our conversations with colleagues indicate that self-experimentation is often conducted secretly today.

The practical and formal authority of an ethics committee over self-experiments is persuasion in most cases. However, obtaining ethics committee approval allows the experimenter to have their work peer reviewed prior to undergoing the experiment. Taking this step also prevents publication problems with journals that require ethics committee review, even though the journals should make an exception for such studies, because doing so is in line with the Helsinki Declaration. We think seeking ethics committee approval should be available, but be voluntary. Ethics committee review for self-experimenters should also be quite simplified and inexpensive. If self-experimentation is formally recognized and review is streamlined, it may be more frequent that self-experimenting scientists seek such review.

By extension, it could make sense that a self-experimenter with ethics committee approval should have a simplified procedure to notify clinical trial regulatory agencies such as the FDA and the European Commission of their intent, and have a venue for reporting data.

### **Appendix - Hippocratic Oath (Ιπποκράτους όρκος)**

## Scientific Self-experimentation Pre-publication Draft

*I swear by Apollo the physician, and Asclepius, and Hygieia and Panacea and all the gods and goddesses as my witnesses, that, according to my ability and judgement, I will keep this Oath and this contract:*

*To hold him who taught me this art equally dear to me as my parents, to be a partner in life with him, and to fulfill his needs when required; to look upon his offspring as equals to my own siblings, and to teach them this art, if they shall wish to learn it, without fee or contract; and that by the set rules, lectures, and every other mode of instruction, I will impart a knowledge of the art to my own sons, and those of my teachers, and to students bound by this contract and having sworn this Oath to the law of medicine, but to no others.*

*I will use those dietary regimens which will benefit my patients according to my greatest ability and judgement, and I will do no harm or injustice to them.*

*I will not give a lethal drug to anyone if I am asked, nor will I advise such a plan; and similarly I will not give a woman a pessary to cause an abortion.*

*In purity and according to divine law will I carry out my life and my art.*

*I will not use the knife, even upon those suffering from stones, but I will leave this to those who are trained in this craft.*

*Into whatever homes I go, I will enter them for the benefit of the sick, avoiding any voluntary act of impropriety or corruption, including the seduction of women or men, whether they are free men or slaves.*

*Whatever I see or hear in the lives of my patients, whether in connection with my professional practice or not, which ought not to be spoken of outside, I will keep secret, as considering all such things to be private.*

*So long as I maintain this Oath faithfully and without corruption, may it be granted to me to partake of life fully and the practice of my art, gaining the respect of all men for all time. However, should I transgress this Oath and violate it, may the opposite be my fate.*  
– National Library of Medicine. Translated by Michael North, 2002.[66]

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