

## Postprint

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# The nature and ethics of natural experiments

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## Abstract

Natural experiments are an important methodology often used to answer research questions that would, otherwise, be impossible to address, or employed because of ethical concerns about the use of randomisation to interventions that carry known risks. The UK Medical Research Council (MRC) recently produced an extremely useful document discussing the nature and significance of natural experiments within medical and public health research. In this paper, however, we suggest that the MRC document's definition of the term 'natural experiment' is insufficiently precise. In response, we offer a taxonomy of different types of natural experiments and related methods, and explore the ethical implications of these different types. We argue that while the ethical issues that may arise within natural experiments in relation to risks of harm or informed consent may differ from those within the randomised controlled trial, they are not thereby less pressing. The implications of the argument are explored and recommendations made for those involved in research governance.

## Introduction

It might be assumed that natural experiments do not raise any ethical issues. Prominent international<sup>1–5</sup> and national<sup>6–8</sup> research ethics guidelines and regulations do not explicitly refer to natural experiments. The literature on the design and use of natural experiments, even major texts,<sup>9,10</sup> appears also to be silent on these issues. It is, therefore, hardly a surprise that the recent guidance from the UK Medical Research Council (MRC) on natural experiments<sup>11</sup> says so little about ethics. Where ethics is mentioned, it is principally by way of suggesting that the choice to conduct a natural experiment obviates certain ethical issues. Thus, discussing the use of the natural experiment in preference to the randomised controlled trial (RCT), the report states: "It may be unethical to manipulate exposure in order to study effects on health if the intervention has other known benefits, if it has been shown to work in other settings, or if its main purpose is to achieve non-health outcomes (p.7).<sup>11</sup>"

The MRC document implies, through the absence of discussion, that natural experiments themselves do not raise any problematic ethical issues. By contrast, in this paper, we argue that at least some natural experiments can create significant ethical issues. First, we begin by suggesting that the MRC

are too quick to treat all kinds of natural experiments as if they were a unified group. We offer instead a twofold classification of natural experiments based on a number of methodological features. Second, based on these distinctions, we can see that at least some natural experiments generate important ethical issues that need to be explored. While we agree with the MRC report that there may well be ethical reasons for choosing to use a natural experiment rather than an RCT, the distinction itself does not eliminate the need to consider relevant ethical issues. Here, we only have space to discuss two of the most significant: issues relating to harms and benefits and considerations relating to informed consent.

### **A typology of natural experiments**

There are many different definitions of the natural experiment available (see appendix 1 of the MRC document<sup>11</sup>). The MRC document itself defines natural experiments as: "events, interventions or policies which are not under the control of researchers, but which are amenable to research which uses the variation in exposure that they generate to analyse their impact (p.4).<sup>11</sup>"

It further states that in a natural experiment 'the intervention is not undertaken for the purposes of research' and that 'variation in exposure and outcomes is analysed using methods that attempt to make causal inferences' (p.4). However, while this definition captures many key features of the natural experiment and distinguishes this design from the 'true' experiment where variables are fully under the control of the researcher—as exemplified by the RCT—it provides an insufficiently precise definition of natural experiments. For example, it does not distinguish this design and the quasi-experiment,<sup>12</sup> and nor does it discriminate between different kinds of natural experiments distinguished according to the different aspects of a study that may be subject to control by the researcher. In order to explore the ethical issues to which natural experiments give rise, one should first establish, and differentiate, the structural features of these different designs.

To consider first the quasi-experiment, this can be thought of as a deliberate, manipulable intervention designed to provide the conditions to observe differences between groups, where assignment to those groups was not random.<sup>12</sup> For example, Haukoos et al<sup>13</sup> evaluated the use of opt-out and opt-in HIV screening in the emergency room of a US hospital. The evaluation was performed in computerised kiosks, programmed for opt-out consent in the first phase of the study, but for opt-in consent in the second phase. In an earlier study, Goetz et al<sup>14</sup> evaluated an intervention designed to increase the rate of HIV testing by introducing it in two Veterans Health Administration facilities while three other facilities served as control sites. In both of these examples, the intervention is able to be manipulated—in terms of its nature, timing, duration and whether it takes place at all. However, allocation of individuals to the arms of the study is not decided randomly, but is predetermined in terms of temporal or geographical patterns of hospital attendance. Although inclusion and exclusion criteria may be specified in a similar way to an RCT, the researcher has to work with predetermined treatment and control groups.

Natural experiments, in contrast, concern interventions that are not fully manipulated by the researcher—the interventions are 'natural' not by way of contrast with 'human' interventions, but to reflect the fact of their not being deliberately manipulated. In contrast to a quasi-experiment, whether the intervention occurs at all is not under the researcher's control in a natural experiment, although other aspects of the study may be (see table 1). In some instances—which we term type 1 ('no control') natural experiments—the intervention being tested is wholly outside the researcher's control. A researcher wishing to study the impact of an earthquake or an epidemic cannot control where it occurs, those whom it affects or when it starts or finishes. Much the same would apply in relation to the impact of national legislation such as licensing regulations,<sup>15</sup> a ban on smoking<sup>16</sup> or on the sale of coal,<sup>17</sup> or the unexpected non-availability of a vaccine.<sup>18</sup> In other cases—which we call type 2 ('partial control') natural experiments—some control of the intervention on the part of the researcher is possible. An example in public health would be a health promotion initiative or a

new form of vaccination. Although whether such measures are introduced is not within the researcher's control, he or she might be able to arrange with the relevant authorities that the programme should be rolled out sequentially in different regions so as to create a control condition, or that it should not be initiated until a certain date, so as to obtain comparative baseline data. In both types of natural experiments, the imperfect level of experimental control sets certain constraints on the measurement of outcome—its timing, frequency and indeed the types of outcomes that can be measured. Therefore, while the researcher can make some decisions regarding the procedures used to measure outcomes within a natural experiment, this is typically to a lesser degree than in an RCT or a quasi-experiment.

**Table 1:**  
Aspects of a study over which experimental control can be exerted, and the degree of such control

	Intervention					Comparator condition	Confounding variables	Measurement
	That it occurs	Where and when	To whom	Its nature	Its termination			
Type 1 natural experiment	None	None	None	None	None	None	None*	Partial
Type 2 natural experiment	None	Partial	Partial	None	None	Partial	Partial	Partial
Quasi-experiment	Full	Partial	Partial	Full	Full	Full	Partial	Full
Randomised controlled trial	Full	Full	Full	Full	Full	Full	Full	Full

\*A degree of statistical control may nonetheless be possible, such as through the use of instrumental variables.<sup>24</sup>

As in the case of the quasi-experiment, the comparison groups in a natural experiment are not formed through random allocation, and so the study does not have the protection from confounding<sup>1</sup> that randomisation confers.<sup>19</sup> In all these non-true experiments, causal inferences, therefore, rely on the assumption that allocation is 'plausibly 'as if' random' (p.282).<sup>20</sup> Thus, in a study of the effect of iron storage on cardiac ischaemia, Germain et al<sup>21</sup> compared individuals who were regular blood donors with those who had been disqualified from donation on the basis of a falsely reactive test for transmissible disease, arguing that such false tests are 'quasi-random'. Such an assumption can always be disputed,<sup>ii</sup> hence, the power of methods employing true randomisation.

Table 1 summarises the dimensions of control possible in the different types of research design. As the degree of control over the conditions of the experiment and over the influence of extraneous variables decreases, so too does the potential internal validity of the study—that is, its ability to make robust causal inferences.<sup>23</sup> In the RCT, subject to some practical constraints, there is potentially full control over the conduct of the study, and it, thereby, has the highest degree of internal validity. The differences between the three types of non-true experiments, which the MRC document does not clearly distinguish, are important. These designs exhibit different methodological characteristics and are, therefore, best treated as distinct so that appropriate steps can be taken to minimise potential bias. In addition to this methodological reason for accepting a more complex typology of natural experiments, there are strong ethical reasons to do so.

## The ethical issues

Given the methodological features of the different types of natural experiments outlined in the previous section, the ethical issues that arise can now be considered. While a number of such issues could be examined, weighing potential harm and benefits and the role of informed consent are perhaps most crucial, and our attention will focus on these, drawing comparisons with the RCT.

### Weighing the risk of potential harms and benefits in natural experiments

Risk of harm to participants is a central concern in the ethics of RCTs, and a primary focus in relevant international research ethics guidelines. The Declaration of Helsinki, for example, states that 'medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects'.<sup>1</sup> In considering harms in research, one can distinguish between an intrinsic risk of harm (one that is an intrinsic feature of the phenomenon being studied, and is, thus, present at the outset of the study) and an adventitious risk of harm (one that arises through unintended or unpredictable, or at least unpredicted, circumstances once the study is underway). Hence, a side effect of a drug that is being tested would be an intrinsic harm, whereas a breach of confidentiality relating to a participant's personal data in such a study would be a potential adventitious harm.

At the core of concerns about intrinsic harms in the RCT is the notion that such a study is an 'artificial' phenomenon, and that any risk of harm that arises within it has, therefore, been created by the investigator. Conversely, it might be thought that a natural experiment comes into being independently of the investigator, and this might seem to absolve the researcher from responsibility for any harm that transpires. However, as noted in table 1, different types of natural experiments allow for different degrees of methodological control. The greater the researcher's capacity to influence the design features of a study, the greater the opportunity to influence the occurrence and magnitude of any potential intrinsic harms, and thereby the greater the responsibility on the researcher to act accordingly.

In a natural experiment, even if researchers are not in a position to control intrinsic harm—and, on the principle of ought implies can, would have no obligation to do so—they should ensure that they respond to adventitious harm, particularly as they may be best placed to identify such harm through the data collection process. Thus, a natural experiment of an infectious disease could exemplify two forms of adventitious harm: it might be noted that the behaviour of some members of the community is placing them at avoidable risk of infection, or that public health measures are being misunderstood or inappropriately applied. It is, also, possible for adventitious harm to derive from the research process; the presence of the researcher, or the way in which data are collected, could give rise to anxiety, or lead to untoward changes in behaviour—possibly based on a misapprehension of the researcher's role—in those observed. Alternatively, the way in which data are handled could lead to harm through a failure fully to observe requirements of anonymity or confidentiality.<sup>25</sup> Accordingly, the investigator may have a duty to respond to potential harm to participants within a natural experiment, just as in any other type of study. For example, there might be a beneficence-based duty to warn if individuals are placing themselves at risk of infection, or a non-maleficence-based duty to take some sort of restorative or compensatory action in the event of harm arising from a neglect of confidentiality. This will have implications for the need to monitor for potential harms within at least some natural experiments, just as in RCTs.<sup>iii</sup>

Given the risk of adventitious harm in at least some natural experiments, the investigator will have the same twofold duty as the trialist conducting an RCT: to minimise such harm and to justify any such harm as remains.<sup>27</sup> The first of these may present a challenge in this context, as a natural experiment is by definition not (fully) under the investigator's control, and the ability to intervene so as to minimise potential harm is thereby limited (depending on the nature and origin of the harm in

question). The investigator may, thus, be in the morally invidious position of perceiving a requirement to act in the interests of research participants' welfare, but having little scope to do so. However, as we saw above, in other cases, such as quasi-experiments and type 2 natural experiments, certain aspects of the research may be under the researcher's control, creating the opportunity for action to minimise potential harm.

The second requirement—justification of any remaining harm—is also potentially problematic. One way in which risk of harm in research is classically justified is in terms of its relationship to the potential countervailing benefits of the study,<sup>1,28</sup> taking due account of the relative extent to which benefits accrue to research participants or to society. Here, a proviso is necessary by way of a distinction between the potential benefits of whatever is being studied and those accruing from the fact of studying it. If the object of study is a public health intervention, just as the investigators are not responsible for any intrinsic harm of such an initiative, they similarly cannot claim credit for its intrinsic benefit. However, any benefits that may arise from investigating this initiative—for example, those arising from its modification in the light of findings from the study and its subsequent rolling out on a broader scale—could play a role in justifying any adventitious harm.

Against this background, the researcher conducting a natural experiment may seem to be at a disadvantage. Given the lesser internal validity of this design vis-à-vis the RCT, evidence of potential benefit may be far less robust, and thus, carry less weight in a justification for risk of harm. Any claim that the potential benefits of the findings from a natural experiment outweigh the potential harms must, therefore, be qualified by the uncertainty that will inevitably surround any such benefits.

However, while the probability of benefit may be unclear, its potential magnitude may be considerable. Natural experiments are frequently used to evaluate interventions whose scale and geographical dispersion make any sort of planned experiment impractical—but this same feature suggests that any benefits arising from the evaluation, and subsequent implementation, of such an intervention may be substantial by virtue of their widespread application. The MRC document gives as examples of phenomena that might be studied through a natural experiment 'the effect of famine on the subsequent health of children exposed in utero, or the effects of clean air legislation, indoor smoking bans, and changes in taxation of alcohol and tobacco' (p.4).<sup>11</sup> The study of each of these has the potential for far-reaching benefit, provided that the information gained from the natural experiment can be translated into appropriate changes in policy or practice.

The category of natural experiments used in the MRC document does not, therefore, correspond to cases where the researcher has no responsibility for possible harms. Where harms can arise, no less explicit a justification is required of these harms than in an RCT, though how potential benefits feature in such a justification may be rather different. Both the investigator and any research ethics committee evaluating a protocol must weigh any potential risks and benefits extremely carefully. Moreover, the extent to which harms can be either prevented or remediated in a natural experiment may, in turn, create ethical challenges. For example, just as the MRC suggests that a natural experiment might be preferable to an RCT for ethical reasons, a concern about harm that could result from an 'as-if random' experiment might influence the choice of method. As an illustration, the effect on accidents of introducing novel traffic calming measures in urban areas could be estimated using a type 1 natural experiment (the researchers are completely independent of the policy makers) or a type 2 natural experiment (the researchers arrange with policy makers to introduce the changes in a gradual way to more effectively answer the research question). Given what we know about the effects of existing traffic calming strategies,<sup>29</sup> it might be argued that any delay in introducing the new measures solely to enhance the robustness of the research is morally problematic. Another example where the methodology may be chosen because of concerns about harm would be a rejection of the use of any quasi-experiment or natural experiment in favour of another design, such as a case-control study.<sup>30</sup> This may be considered preferable as retrospective studies are less likely to raise concerns about intrinsic or adventitious harms.<sup>iv</sup>

### Informed consent and participation in natural experiments

Informed consent has a similarly central role in research ethics to that of risk of harm, and similar prominence in research ethics guidelines, where it is commonly regarded as a moral prerequisite for a study to take place.<sup>1,5</sup> Only rarely is consent seen as a negotiable requirement.<sup>31</sup> Seeking informed consent is traditionally held to be a means of respecting an individual's autonomy, and in the context of participation in research, it provides a permission or justification for involving that individual. For example, Holm and Madsen (p.12)<sup>32</sup> suggest that 'the basic idea of informed consent is that a researcher is only (ethically and/or legally) justified in using a research subject in a project if the research subject has consented to being so used'.

Here, consent is seen as a licence for the researcher to do something to research participants; for example, to randomise them to two or more alternative treatments. In a natural experiment, in contrast to an RCT or a quasi-experiment, the intervention or phenomenon under study is one that may take place without the investigator's involvement, and the issue of doing something to participants seems not to arise. It may be that the issue of consent is not mentioned in the MRC document because it is not seen as necessary for this reason. Again, however, things are, perhaps, more complicated than this suggests. In at least some natural experiments, researchers are not doing anything to participants, but they may well know that preventable negative outcomes may occur if circumstances change during the study. In such cases, researchers would be unwise to rely on the idea that such consequences were the result of what they allowed to happen, rather than what they did or intended to do.<sup>v</sup> Leaving to one side the many ethical issues that it raises, an aspect of the Tuskegee syphilis study—in which the natural progression of the disease was monitored in a sample of African-American men—is instructive as a way to see the importance of the distinction.<sup>34</sup> Once treatment options became available during the study, the researchers' failure to intervene is a case of adventitious harm for which they were responsible; moreover, their responsibility is heightened by the fact that participants were not made aware of this new information, and could not, therefore, make a decision on continued involvement in the study.

So, it should not be assumed that there is no role for consent in relation to natural experiments, but nor do we suggest that informed consent is always required prior to the involvement of every participant, particularly in public health or other community-level research.<sup>35</sup> Each proposed study should be considered on an individual basis. Often, consent to the receipt of an intervention within the context of a natural experiment will not be possible. However, the consent requirement may persist in relation to data collection, unless such information is publicly available or aggregated, and need not, therefore, be collected from individuals. Thus, Costello et al <sup>36</sup> studied the effect of a change in family income on children's mental health via annual psychiatric assessments, for which, individual consent would be required, whereas Herttua et al <sup>37</sup> used available mortality register data to study the effect of changes in the price of alcohol on mortality, with no requirement for individual consent.

Moreover, even if the 'consent' component of informed consent does not come into play as a form of authorisation, the need to 'inform' may remain, as the latter may be as important as the former as a means of protecting an individual's autonomy. If new information arises during the course of a natural experiment that has implications for the welfare or autonomy of those being studied, and these implications are sufficiently serious, the researcher may be obliged to convey this information as part of a duty to warn. This obligation may be heightened where individual participants are readily identifiable (suggesting that the information can be passed on promptly and effectively) and where some sort of relationship has been established between participant and the researcher, such as where information has been previously collected at an individual level. However, the obligation to disclose information need not depend on either of these considerations; the simple fact that the researcher has come into possession of information that bears on participants' well-being places an a priori onus on the researcher to act in response to this.

The fact that consent to an intervention is likely not to be feasible in at least some natural experiments (e.g., type 1) gives rise to an ethical problem relating to risk of harm. The role of a harm–benefit calculation as a justification of risk of harm has already been explored. An additional argument is that potential harms are justified to the extent that they are consented to (and to the extent that we can overcome the difficulties of obtaining the necessary levels of comprehension and recall on the part of the participant<sup>38</sup>). Consent here is construed as a necessary condition, even if not a sufficient condition, for exposing individuals to risk of harm.<sup>vi</sup> The impossibility, in most cases, of obtaining consent to an intervention that is the subject of a natural experiment removes, therefore, its justificatory role in relation to risk of adventitious harm. Thus, the removal of one moral requirement heightens another: accepting that consent is not morally required in such circumstances also means that the researcher cannot appeal to consent as a moral justification for any risk of harm. The researcher may, therefore, have to compensate for the absence of this function of consent in some other way.

It is certainly the case that many interventions suited to evaluation through a natural experiment—particularly within public health—may be ones for which members of the public would not normally expect their individual consent to be sought.<sup>39</sup> One possible way to compensate here for the absence of consent—and the consequent absence of its justificatory role in respect of harm—would be to set a low threshold for the possible harms in question and see an obligation as being placed upon the researchers to constantly monitor for such harms. Any research ethics committee would be under a corresponding obligation to assure itself that such monitoring was to be undertaken. A second option would be to explore other indirect means of determining the acceptability of the research to the participants, perhaps through different forms of community consent, community engagement or hypothetical ‘consent’. However, there are good reasons to think that such methods are a poor substitute for consent, at least in terms of the role of authorisation.<sup>39</sup> Investigators should certainly not just assume that because their research uses a natural experiment, there are no issues relating to consent, and research ethics committees and researchers should consider, prior to a study being conducted, how they should address such issues.

## **Conclusion**

The term ‘natural experiment’ is one that tends to be used imprecisely. The taxonomy offered in this paper provides a means of distinguishing different types of natural experiments. Such distinctions are not of mere academic interest, as these different types have both methodological and ethical implications; some key issues in relation to the latter are summarised in table 2. Certain elements of at least some natural experiments can potentially be controlled or influenced by the researchers, so it does not follow that they are automatically absolved of ethical responsibility. While the ethical issues that may arise in relation to risks of harm or informed consent may differ from those of the RCT, they are not thereby less pressing. One general governance issue that arises from this discussion is how to deal with the emergence of adventitious risk during a natural experiment. The use of an oversight committee performing a similar role to that of a data monitoring committee would be one option. Such a recommendation might be seen by some as excessive and bureaucratic, but on the other hand, it provides an important safeguard for participants, and this is particularly important where individuals do not or cannot consent to participate in such studies. In addition, ethical guidelines specific to natural experiments could usefully be developed to help researchers and research ethics committees to identify and deliberate about the important ethical issues that can arise in the use of this valuable research design.

**Table 2: Summary of ethical implications of risk of harm and informed consent in relation to type 1 and type 2 natural experiments**

		Risk of harm		Informed consent	
		Intrinsic harms	Adventitious harms	Consent to an intervention	Consent to data collection
Type 1 natural experiment	Researcher has no control over these harms, and thus, no duty is placed on the researcher to respond to them		The researcher may be able to control, and thus prevent or limit, adventitious harms, and will, therefore, have a duty to do so, and to justify any risk of such harm that remains	Lack of control over the intervention removes the need to seek consent, but a duty to inform may persist in relation to risks and consequences of participation	Unless the data are already in a publicly available or aggregate form, consent to their collection is <i>prima facie</i> required
Type 2 natural experiment	Researcher has limited control over these harms and thus has a correspondingly limited duty to respond			The greater the control over the intervention, the greater the opportunity to inform (particularly if participants are more readily identifiable than in a type 1 natural experiment)	

**Footnotes**

- i. Confounding refers to the presence of an extraneous variable that has a statistical association with both (a) the factor being tested in an experiment (ie, the groups defined by the intervention variable) and (b) the outcome of interest, such that the estimate of the between-group difference in the outcome is (potentially) biased. These two statistical associations involving the extraneous variable are joint necessary conditions for confounding; as randomisation obviates (at least asymptotically) an association between the extraneous variable and the factor, it thereby obviates confounding.
- ii. While the assumption is always contestable, its plausibility depends on the circumstances of the study. In some instances, these may strongly favour the ‘as if random’ presupposition. Thus, Dunning<sup>20</sup> cites a study by Doherty et al<sup>22</sup> in which the social and political attitudes of lottery winners were compared; lotteries are random processes, and there is, consequently, a very high degree of randomness (although not total) in the separation of winners and non-winners. In other situations, the ‘as if random’ assumption may be more speculative.
- iii. In practical terms, it might be appropriate to consider implementing a data monitoring committee and to determine stopping rules, based on interim analyses, for any preventable harms.<sup>26</sup>
- iv. In a case–control study design, groups are defined in terms of their either having (cases) or not having (controls) the outcome of interest. These groups are then compared statistically in terms of their relative prior exposure to a potential causative factor. As the exposure predates the study, the researcher is not responsible for its occurring or for any associated harms.
- v. The literature on the doing/allowing distinction is vast and primarily focused on whether doing harm is somehow worse than allowing a harm to occur. Intuitions and moral theories will differ about what answer they give to this question.<sup>33</sup> Our caution to researchers here does not require that there is strict equivalent moral value to be assigned to the outcomes of doing and allowing, but rather that there is at least sometimes moral responsibility for known potentially harmful outcomes. This less demanding requirement is generally seen to



impose a strong obligation to act to prevent harm, at least in research ethics. For example, where a researcher comes to believe that one treatment option is demonstrated to be preferable, equipoise is disturbed and action is required. Where a researcher does not act, an appeal to the fact that the harm was only allowed to happen will not excuse (at least some) responsibility for the outcome.

- vi. In instances where risk of harm is of very slight magnitude (e.g., constituting little more than inconvenience), consent might not even be a necessary condition.

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