Understanding individualised genetic interventions as research-treatment hybrids

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Received 22 November 2023
Accepted 6 June 2024

To cite: Johnston J, Tabb K, Pacia D, *et al*. *J Med Ethics* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jme-2023-109729

ABSTRACT

Until recently, medicine has had little to offer most of the millions of patients suffering from rare and ultrarare genetic conditions. But the development in 2019 of Milasen, the first genetic intervention developed for and administered to a single patient suffering from an ultrarare genetic disorder, has offered hope to patients and families. In addition, Milasen raised a series of conceptual and ethical questions about how individualised genetic interventions should be developed, assessed for safety and efficacy and financially supported. The answers to these questions depend in large part on whether individualised therapies are understood as human subjects research or clinical innovation, different domains of biomedicine that are regulated by different modes of oversight, funding and professional norms. In this article, with development and administration of the drug Milasen as our case study, we argue that at least some individualised genetic therapies are not, as some have argued, either research or treatment. Instead, they are research-treatment hybrids, a category that has both epistemological and pragmatic repercussions for funding, ethics oversight and regulation.

INTRODUCTION

Taken collectively, rare genetic diseases are common. In the USA, approximately 7000 different rare conditions (diseases that affect fewer than 200 000 people)[1] taken in aggregate affect as much as 10% of the population.[2] Even ultrarare diseases, a subcategory with no official regulatory definition that has been described as comprising conditions known to affect 30 or fewer individuals, are thought to afflict millions worldwide.[3] For a long time, medicine has had little to offer these patients beyond, in some cases, a genetic diagnosis, which can refine health surveillance. But the development in 2019 of Milasen, the first genetic intervention designed for and administered to a single patient suffering from an ultrarare genetic disorder, has offered some hope to patients and families.

Milasen is an antisense oligonucleotide (ASO)—a short nucleic acid molecule that in this case is intended to change the splicing of a disease-causing gene.[4] Along with gene addition and gene editing approaches, ASOs like Milasen offer a pathway for realising the promise of precision medicine for people with the rarest of genetic conditions. In addition to hope for patients and their families, however, the advent of extremely individualised genetic therapies[i] raises a series of conceptual and ethical questions about how these interventions should be developed, assessed for safety and efficacy and financially supported.[5 6] The answers to these questions depend in large part on whether use of individualised therapies is understood as human subjects research or clinical innovation: two different domains of biomedicine with different modes of oversight, funding and professional norms (see figure 1). Here, with development and administration of the drug Milasen as our case study, we argue that at least some individualised genetic therapies are not solely research or solely treatment; they are both. We call them *research-treatment hybrids*—a novel category that has both epistemological and pragmatic repercussions for funding, ethics oversight and regulation.

THE MILASEN CASE STUDY

At 6 years old, Mila Makovec was diagnosed with an extremely rare, rapidly progressive neurological disorder called Batten's disease. In less than a year, a team of 48 clinicians and researchers led by Dr Timothy Yu of Boston Children's Hospital had identified the specific genetic variant causing Mila's condition—a retrotransposon that disrupted RNA splicing.[7] Mila was the first known case of Batten's disease with this particular genetic cause.[4] Yu's research team designed an ASO to correct her unique splicing defect, testing the effectiveness of the ASO in fibroblasts cultured from the patient and assessing its potential toxicity in rats. Just a month

[i]The clinicians and scientists who reported the development and administration of Milasen in *NEJM* called it an 'n-of-1 clinical study', language that has since been used by others. Although individualised interventions like Milasen do often involve a single patient or research participant, and may technically have an 'n' of 1, they differ markedly from what have historically been referred to as n-of-1 approaches. (See Kravitz RL, Duan N, eds, and the DEcIDE Methods Center N-of-1 Guidance Panel; Duan N, Eslick I, Gabler NB, Kaplan HC, Kravitz RL, Larson EB, Pace WD, Schmid CH, Sim I, Vohra S; and Design and Implementation of N-of-1 Trials: A User's Guide. AHRQ Publication No 13(14)-EHC122-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014.) While patients like the child in the Milasen case do serve as their own controls, in the sense that the effect of the intervention is measured against their preintervention baseline, they do not switch between active and inactive arms, or between different active arms; they also may not have a chronic or stable condition—indeed at this early stage, these interventions are most likely to be used in patients whose condition is life threatening and rapidly progressive. We, therefore, do not adopt 'n-of-1' terminology, preferring instead 'individualized genetic interventions'.

	Research Features	Clinical Care Features
Oversight	Development of the ASO was overseen by Boston Children's Hospital's IRB for the collection of cells from the patient.	Administration of the intervention took place without formal IRB review (although with the knowledge and concurrence of the IRB chair).
Regulation	FDA was involved in approval.	Expanded access pathway was used instead of the typical regulatory pathways.
Clinician-Investigator Intentions	Investigators hoped Milasen would model approaches applicable to other patients (i.e., development of a template or pathway).	Clinicians developed and administered Milasen to a specific patient based on her clinical need with intention to improve her health.
Funding Mechanism	Intervention was supported by Boston Children's Hospital Translational Research Program.	Intervention was funded by Mila's Miracle Foundation, a charity founded by Mila Makovec's family, that has an explicit goal of bringing individualized interventions to other patients.

Figure 1 Research and treatment features of the Milasen case. ASO, antisense oligonucleotide; FDA, Food and Drug Administration; IRB, Institutional Review Board.

later, in early 2018, the team sought and received permission from the Food and Drug Administration (FDA) to begin administering the ASO to Mila. Over the next 2 years, following repeated administration of Milasen, the patient's family reported a decrease in Mila's seizure frequency.[4] While Milasen improved Mila's quality of life, it did not cure her disease. Mila Makovec died in February 2021 at the age of 10.

The oversight and regulatory approaches applied to Milasen were a complex and alternating mix of human subjects research and clinical innovation processes. To develop the ASO, researchers needed to collect blood and skin cells from Mila. This aspect was understood as human subjects research, overseen by the Boston Children's Institutional Review Board (IRB). Yet, at the point of administration, Milasen appears to have been treated as a clinical intervention, although a novel one. Although Mila's doctors obtained the concurrence of the IRB chair, Mila received the intervention under an expanded access approval from the FDA, an exception to usual FDA regulations for patients not eligible for an ongoing clinical trial. Access in these cases is driven by clinical need, and patients under an expanded use approval are not research subjects. But in the Milasen case, there was no clinical trial—the single expanded access patient was the only person receiving the intervention, a fact that was clear to the FDA.

Funding for development of Milasen was also a research-treatment mix, coming from the Boston Children's Hospital Translational Research Program and the Mila's Miracle Foundation, a charity founded by the patient's family to pursue a treatment for Mila and other children with rare diseases. The researchers and clinicians involved in the development and administration of Milasen understood its importance for other clinicians, researchers and patients, writing a manuscript for the *New England Journal of Medicine* describing the case and stating that they hoped it would serve as 'a possible template for the rapid development of patient-customized treatments'.[4]

In the time since Yu's team reported their work, Milasen has become a model for new individualised genetic interventions, developed to treat specific patients using potentially replicable intervention development pathways. There are three main types of genetically targeted, individualised interventions in development: approaches similar to Milasen that seek to impact splicing or gene expression using synthetic strands of DNA or RNA; 'gene addition' approaches that use viral vectors or other delivery methods to add a functional copy of a gene in patients with loss-of-function mutations[8]; and 'gene editing' approaches that use CRISPR or other technologies to edit or alter patients' genes.[9] The hope is that all three types of novel interventions can be tailored to rare genetic variants that affect a single or a small number of patients, many of them children.[10]

A number of scientific questions are raised by Milasen and other individualised genetic interventions. Are they safe and effective? Can early examples serve as models for subsequent patients, yielding well-defined intervention development pathways? These questions quickly lead to oversight, ethics and regulatory ones. Can such pathways be reviewed through existing oversight and regulatory systems, or must each intervention be assessed as a new investigational drug or biologic? When discussing these interventions with patients, should clinicians wear their researcher 'hat', emphasising risks and working to address any therapeutic misconception on the part of the research subject, or should they work as clinicians pursuing innovation with patients who they genuinely believe might benefit from the interventions? Who should fund this work? Who should oversee it? At what point is there sufficient evidence to consider the intervention safe and effective? While often not posed explicitly, the answers to such questions hinge on whether individualised genetic interventions are understood to be treatment or clinical research.

If their development and administration is human subjects research, they will be overseen by research ethics committees such as IRBs in the USA, with stopping rules, conflict of interest requirements, research-focused informed consent procedures and other features designed to protect participants from harm while enabling the systematic accumulation and dissemination of knowledge.[11] If they are instead understood as novel clinical treatments, then risk-benefit analyses will reflect patient-clinician negotiated goals of care and ethical guidance, and oversight will be drawn from clinical ethics, rather than the formal, prospective review processes applied to research. If they are research, their development and administration might be supported by biomedical research funders, as well as government bodies that support basic science, translational and clinical research. If they are treatment, patients and their families will likely provide the majority of the financial support needed for their development and administration, although insurance companies will increasingly be petitioned to cover them.

MILASEN AND THE TREATMENT-RESEARCH DICHOTOMY

One interpretation of the development and administration of Milasen is that the process is merely an example of clinical innovation similar to a new surgical technique developed in response to the unusual anatomy of a particular patient.[12] This appears to be the approach taken by European regulators, with clinicians reportedly able to request hospital ethics committee approvals to develop and administer Milasen-like interventions on a 'named-patient' basis.[13] Under the umbrella of clinical medicine, such innovations are created and administered to serve the best interests of individual patients. This patient-centred focus can be contrasted with research, where there is typically said to be no expectation of direct benefit. Indeed, research participants who believe, contrary to the information they are given, that they necessarily will benefit from participation in research are said to be under a therapeutic misconception.[14]

In the Milasen case, Mila's parents and doctors had reasons to hope for direct clinical benefit. But they also hoped that it would

generate knowledge to advance a field, an understanding shared by the parents, IRB members and clinical geneticists we interviewed about this kind of intervention, who overwhelmingly reported their hopes that such interventions would both benefit the specific patient and generate knowledge useful for others.[15] Characterising an intervention like Milasen purely as clinical medicine would conflict with the insights of these stakeholders. It would also risk failing to record and capture adequately the knowledge gained and lessons learnt from the development and administration process. A purely clinical classification could also recapitulate the ethical challenges associated with innovative surgeries and other novel clinical interventions, leaving patients potentially exposed to levels of risk that would not be tolerated in research and without independent oversight.[10]

An alternative understanding sees Milasen and similar interventions as a form of clinical research. Something approaching this position seems to be held by regulatory bodies in the USA, which in 2021 (ie, after the Milasen case) asserted the requirement of formal research ethics review before similar interventions are administered to patients.[16] This position also finds support in the academic literature, for example, from Kane *et al* who have argued that while individualised therapies 'are sometimes perceived as dissolving tensions between the goals of research and care', they should be strictly understood as a form of research.[6] On their view, the development of Milasen was clearly intended to model an approach or algorithm that, with small modifications, could be applied to other patients. 'What we want to know' in a case like Milasen, they argue, 'is not merely whether an individual patient benefits, but whether the intervention algorithm has potential, when applied to a series of patients, to bring about outcomes that are better than with alternative treatments'.[6] As such, they argue, the process aims to generate generalisable knowledge and therefore constitutes research. This interpretation fits with some of the goals expressed by the stakeholders we interviewed, who supported gleaning as much as possible from each individualised genetic intervention for the benefit of other patients with rare diseases. Yet, the dominant approach to generalisability is not a neat fit with this kind of intervention.

GENERALISABILITY AS A VALUE FOR RESEARCH

In the USA, federal regulations define research as 'a systematic investigation, including development, testing, and evaluation, designed to develop or contribute to generalizable knowledge'.[17] If a study aims at generalisable knowledge—and if human subjects are involved—the research ethics review process is triggered, which when a drug, device or biologic is involved, in turn enables the establishment of an evidence base for FDA approval. In clinical research, knowledge is typically understood to involve information about the safety and efficacy of the intervention itself, or possibly a method for its administration. Such knowledge is 'generalizable' if it has *external validity*—that is, if the findings apply to patients in the general population who fall under the same classification as those in the study sample.[17] To demonstrate that knowledge is generalisable, clinical research traditionally involves group comparison studies, with the randomised controlled trial (RCT) as the gold standard. A large sample can provide the necessary power to detect even a small effect, and translational medicine has diverse strategies for shaping experimental conditions to accurately represent relevant aspects of the real world.

Study designs like the RCT are not feasible when interventions are developed for a single patient, who may be the only person ever to receive the particular intervention or who may be the first of a very small number. Although development of an individualised intervention can be done systematically—for example, according to a prospective plan that incorporates testing and evaluation to answer defined questions and assess specific outcomes—there will be no control group, or if there is, both groups will be very small. Furthermore, assessing the external validity of an intervention, already a challenge given the difficulty of reproducing the diversity of clinical populations in experimental settings, is a non-starter in individualised therapies where all, or the vast majority, of known cases are already included as subjects of the intervention. If external validity for a particular class of disease is the sole appropriate measure for assessing generalisability—and generalisability is taken to be a defining factor of research—then cases like the development and administration of Milasen will not be considered research.

But there is debate over whether external validity should be the sole or most meaningful proxy for generalisability. Some philosophers and scientists emphasise instead that small studies based on careful causal reasoning can generate valuable new knowledge by demystifying complex biological processes that cross-cut individual medical conditions.[18] For example, writing about the meaning of generalisability in the context of neurological research, Kukull and Ganguli argue that 'even very narrowly defined study samples may provide widely generalizable results if conducted with an eye to rigorous internal validity', that is, if care is taken that the study design correctly targets the variables it sets out to measure.[19] Hekler and colleagues, in a paper responding to the development of personalised medicine, have called for a 'small data paradigm' that can rigorously use 'data by and for a specific N-of-1 unit'.[20] Although such studies may not produce generalisable knowledge in the traditional sense, Hekler and colleagues argue that knowledge capable of guiding future interventions can be generated; they call this kind of knowledge 'transportable'.

Suspicion about traditional standards for establishing generalisability, and thus about traditional means of demarcating clinical research from clinical practice, is in part brought on by shifts in dominant methodologies characteristic of the precision medicine paradigm. Individualised interventions draw on the extreme ends of the spectrum, often using 'big data' to discover genetic anomalies and then 'small data' to test new therapeutics. They cannot appeal to traditional measures of validity that rely on an abstract disease construct. As such, they challenge the traditional view that generalisability can only be assessed using external validity measures. However, there are many transferable lessons from cases like Milasen applicable to other conditions with a similar genetic cause, or where the same method of intervention delivery is being considered, or where similar methods to monitor outcomes are needed. In our empirical study of stakeholder perspectives, IRB members argued for a more expansive view of generalisability to include various types of information that could benefit unknown future patients.[15]

Expanding generalisability beyond external validity should have repercussions for the way in which studies are funded and regulated, with additional measures needed to assess their value outside the discovery context. The philosopher of medicine Lara Keuck has offered a new measure of 'scope validity' to refine how we assess the potential for an experimental model to be applied to a population beyond that used for discovery.[21] Instead of focusing on the external validity of disease constructs when evaluating the validity of biomedical results, Keuck argues, the possibility for generalisability often comes into better focus when attention is paid to the more fine-grained aspects of the

experimental model and/or the patient population. Instead of offering a totalising assessment of generalisability, then, scope validity aims to specify targets where the results of a study will be *locally* generalisable. In individualised therapy studies, where disease constructs are often irrelevant given the uniqueness of patients' conditions, external validity with respect to a general patient population is most likely irrelevant, and critical attention to scope becomes crucial. For example, in the Milasen case, an assessment of scope validity might focus attention on the potential for aspects of that drug's development pathway to be generalised to other therapeutic targets with similar, but not identical, characteristics. As Keuck notes, a consideration of scope validity could estimate the extent to which the development of an experimental drug with no immediate transformative effects on healthcare nonetheless might serve medicine's general aim of being useful for the many, not just the few.

Oversight	Development of the intervention and its administration will likely need to be overseen by a human subjects research committee, such as an IRB, with involvement of a clinical ethics committee or consultants.
Regulation	Laws or regulations for human subjects research and drug approval (e.g., as administered by the FDA) as well as legally enforceable standards of care may apply to the development and administration of the intervention.
Clinician-Investigator Intentions	The mix of therapeutic and research goals is transparent and recognized as valid. Aspects of the protocol with primarily therapeutic goals (such as patient selection) or primarily research goals (such as informed consent) are managed by team-members whose focus is also primarily therapeutic or research, respectively.
Funding Mechanisms	A translational research funder might be most appropriate. Innovative funding partnerships between, for instance, biomedical research funders and insurers or disease advocacy groups could be explored.

Figure 2 Potential oversight and ethics implications of hybridity. FDA, Food and Drug Administration; IRB, Institutional Review Board.

MILASEN AS A RESEARCH-TREATMENT HYBRID

We propose that development and administration of Milasen and other individualised genetic interventions be recognised as both research *and* treatment—that is, as *research-treatment hybrids* (see figure 1). This hybridity may come through in the aims of each intervention, which might simultaneously include the production of generalisable knowledge *and* benefiting the patient therapeutically; their methods, which might draw on traditional study designs as well as clinical care protocols; their funding, which might be provided by designated research dollars and clinical care payment mechanisms such as insurance or patient's own funds; and their ethics and oversight, which might involve IRBs applying the rules of human subjects research and clinical ethics services navigating the ethics of clinician–patient relationships.

Recognising Milasen and similar interventions as research-treatment hybrids is descriptive rather than prescriptive; we believe that individualised genetic treatment studies have already, implicitly, taken this form. Nevertheless, our account has normative implications; chiefly that it more accurately reflects key stakeholders' therapeutic and knowledge generation goals. In our interviews with family members of children with rare genetic disorders, geneticists and IRB members, we explicitly asked them whether they understood these novel individualised interventions to be research or treatment, and most reported that they were both.[15] Families in particular found the question odd, emphasising both their desire to help their child and the hope that knowledge learnt could help others. These results support hybridity as a description, and descriptive accuracy in turn increases the likelihood that those directly involved in development and administration will recognise their own experience in the language used to describe these interventions, as well as in the ethical and regulatory tools supporting their use.

We should expect that this hybridity will take a different form in each case; individualised genetic interventions form a heterogenous class. Accordingly, this analysis does not amount to an evasion of the challenge of sorting out what individualised genetic treatments are by merely answering 'both'. The regulatory and ethical challenges that characterise this class should be met by establishing the unique hybrid nature of each case. If, as we suspect, individualised interventions vary in the research and clinical aspects they assume, there may be no simple answer to how they should be funded, overseen and regulated; such decisions will need to be taken on a case-by-case basis. At the same time, recognising them as aggregates of research and clinical paradigms, rather than new and emergent sorts of studies, should enable patients, clinicians, researchers, institutions and regulators to draw on the best of both paradigms to better understand and address the ethical and legal questions these interventions raise, preserving the foci of clinical ethics (patient-centredness, an emphasis on communication and compassion, and the involvement of family) while incorporating protections from research oversight (see figure 2).

Regarding expectations of benefit, for example, hybridity validates the clinical ambitions of providers and the therapeutic expectations of patients and families. Similarly, hybridity allows for the expectation that patient selection will be driven by clinical judgement: patients are selected based at least in part on the hope that they will benefit. Hybridity also recognises and perhaps even validates the dual roles of clinician-researchers who, like Yu, are involved in care of the patient and design and administration of the individualised therapy. Recognising these roles does not mean throwing out traditional research-related precautions: there may still be a need for a research-only or independent colleague familiar with the condition and risks and benefits of the therapy to obtain informed consent, for example. Instead, it serves to highlight non-judgementally the inevitable tensions and complexities that can face the clinician-researcher and to introduce a mix of mechanisms for managing them.

That said, hybridity does introduce complications. Consent processes may become more detailed when they must acknowledge patients and families' expectations of benefit, while also emphasising uncertainty of response, novelty and risk. There may be heightened risk that the research nature of the protocols will be downplayed or not sufficiently appreciated by patients who are focused on the therapeutic prospects. Oversight may also be more burdensome if studies need to undergo both research and clinical ethics review. One response might be to develop a form of specialised review that combines both approaches. Indeed, where cases share complex scientific or clinical features, there might be value in a specialised national review group. At this time, the FDA has made clear that it expects IRB review of these cases, a requirement that perhaps reflects the agency's understanding that some IRBs might think individualised therapies do not meet the legal definition of research—regardless, the FDA wants to see research-level protections.

Regarding funding, categorising the development and administration of at least some individualised therapies as a type of research may open access to public research funds. This would be a welcome development for patients and families who are otherwise left to raise these funds themselves. We note, however, that while the development and administration of individualised

therapies like Milasen might count as research, this does not settle questions about the value of their development when compared with other possible uses of limited research funds. Genomics in general, and precision medicine in particular, receive extensive criticism on healthcare equity and distributional justice grounds that can only be partially addressed by reference to the generalisable knowledge these activities might generate.[22–25] At least initially, individualised genetic therapies are likely to benefit disproportionately already advantaged individuals who can participate in such studies. That said, recognising that some such studies have broader scope could demonstrate how their development might attenuate these inequalities.

CONCLUSION

The Milasen case is an example of a research-treatment hybrid: an individualised genetic intervention that was both designed to benefit a particular patient and intended to generate knowledge that can be applied to other patients with different genetic conditions. It was a case driven by clinical judgement and shaped by clinical ethics—a case where clinicians worked to relieve suffering through the development and administration of a novel therapy that they, and the patient's family, very much hoped would provide direct benefit. It was also a case driven by the search for scientific knowledge and shaped by research ethics and research regulations. Milasen represents, therefore, not only a milestone in precision medicine but a chance to enrich our understanding of what is considered research, and what types of knowledge gains can come from different intervention development pathways.

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Contributors JJ, KT and DP conceptualised and drafted the manuscript as part of a team project involving SS-JL, WKC and PSA and for which PSA is the principal investigator. The article draws on empirical research conducted by this same team. Drafts of the article were edited by all authors multiple times. JJ can act as guarantor regarding the veracity of this statement.

Funding This study was funded by the National Human Genome Research Institute (grant number: 3RM1HG007257-08S1).

Competing interests WKC is on the Board of Directors for Prime Medicine and the Board of Directors for Rallybio.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. This manuscript does not present new data. Any data or research referred to in the manuscript is published as cited via a reference.

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