**The ethics of child participation in significantly risky non-therapeutic research**

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Imagine that a research group has just created what they think is an effective Ebola hemorrhagic fever vaccine. It has been tested in adults, found to work as expected, and caused no deaths among the participants (despite having the known potential, say, to cause death with some arbitrarily low chance). Imagine further that to see the public health benefits we want (eradication of the virus or stopping its spread), we will need to vaccinate children as well as adults. Thus, we must recruit healthy children for a safety study like that which we have just done in adults. The only problem is that the vaccine still has the same potential to cause death, and perhaps has other unknown risks. Should we allow such a study to be undertaken? Here I will argue that yes, we should allow such a study, and studies on children like these which are significantly risky and nontherapeutic. Specifically, I will argue that children (like adults) should have a basic preparedness to contribute to their society and advance a community's interest, even when such a contribution exposes them to a significant or unknown level of risk. To make this claim I will first demonstrate that children are regularly exposed to risks and that we justify this exposure in ways that could be transferred into the context of nontherapeutic research risks. I will then argue that children (like adults) have an interest in public health, indirectly benefit from good public health, and share in the bounties of advancements made in the biomedical sciences (which are made possible via research of various natures, including nontherapeutic research). Further, children above a certain age have some capacity to consent to such research, and such consent is ethically significant. To the extent that they don't have capacity to consent, however, parents, carers, and medical professionals can reliably determine what is likely to be in the child's best interests, and therefore what study or studies it is reasonable for that child to be a subject in. To frame my argument, I will use the aforementioned example of a vaccine for Ebola hemorrhagic fever, a virus that is currently ravaging large parts of

West Africa and causing devastating human and public health consequences. I will also expand upon the ethical issues generated by this case and consider whether other cases could be justified based on the principles established.

Children are a vulnerable population. They instinctively trust the adults who care for them and rely on their judgement, from where to go to school to which treatment option is best for them in cases of serious illness. If they are fortunate enough to have responsible and moral adults caring for them, they have a relatively happy and healthy existence in return for this trust. This arrangement gradually fades as the child ages, until they are old enough to make their own decisions. Research involving children is therefore immediately problematic for their adult carers and those tasked with obtaining consent for the research. How can we be sure it is in their best interests? What are their values, or do they have the capacity to hold sincere values at all? If so, would they be relevant? And if they could give consent, to what extent should we consider that consent meaningful or well-informed? These and other questions complicate ethical decision-making in human research involving children, however are much easier with certain answers. For example, if the research is therapeutic, and especially if the child is beginning to run out of medical options (as is sadly the case in many instances of paediatric cancers or other terminal illnesses), it is far easier to justify the research. This therefore demonstrates that the potential problems of consent and risk can be overcome by particular circumstances. Any risk- or consent-related problems are intuited as being justifiably ignored due to a set of particular circumstances - namely when it is only being ignored with the end goal of directly benefiting the child in question. However, we cannot dismiss the possibility of other sets of particular circumstances, where the benefit is less direct or purposely directed towards the child in question (like in personalised medicine), justifying the same. This is not to say that all nontherapeutic research on children is justified, just that in certain, particular circumstances, it may be. To determine these circumstances, we should first examine if less direct benefits (as compared to more direct benefits) can justify ignoring particular levels of risk- or consent-based problems for such research.

Let's first deal with risk: By what normative reasoning could we justify asking a child to expose themselves to risk of harm when they are otherwise safe and in good health? Perhaps they would be the same normative reasons we use to justify our allowing children to ride in the car with us to get to school or go shopping. Or perhaps it would be the same normative reasoning which justifies us enrolling children in sports programs. Almost all of our everyday activities involve some level of risk, including those which children participate in[1]. Additionally, children and adolescents tend to engage in risky behaviours, like jumping from high playground equipment[2] and participating in unprotected sex[3]. These risk-taking activities are common and have probable developmental importance and explanations[4][5]. Should that mean we can justify exposing children and adolescents to higher levels of risk than adults? Probably not, since many of the risky behaviours that children and adolescents engage in are behaviours or risks which we would otherwise wish to minimise if we were able to (and we in fact do make attempts to, for example, make playgrounds safer for children and encourage adolescents to observe safe-sex practices). In other words, we do not find these risks fully acceptable. Thus, we may not use these particularly risky categories of activity, which children and adolescents would ideally avoid, to justify asking them to engage in nontherapeutic research of a similar risk level (as we do not find such levels of risk justifiable generally). We could still use categories of activity which we are normally happy for children and adolescents to be engaged in,

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[1] 'Risk-Benefit Assessment in Pediatric Research' Sumeeta Varma, David Wendler in *The Oxford Textbook of Clinical Research Ethics* Ezekiel Emanuel *et al.* (eds), 2008, Oxford University Press, p. 531.

[2] 'Risky Play and Children's Safety: Balancing Priorities for Optimal Child Development' Mariana Brussoni, Lise Olsen, Ian Pike, David Sleet. *International Journal of Environmental Research and Public Health*, 2012, v. 9 (9), p. 3135.

[3] 'A Social Neuroscience Perspective on Adolescent Risk-Taking' Laurence Steinberg. *Developmental Review*, v. 28 (1), p. 78.

[4] *Ibid 2*. p. 3136.

[5] *Ibid 3.* p. 82.

such as riding in a car or playing sports. However, such activities probably do not share the same risk likelihoods or potential levels for serious harms as those likely to appear in significantly risky nontherapeutic research, though in practice this would need to be determined a case-by-case basis. A child's risk of severe (organ failure or permanent damage) or catastrophic (death or comatose state) harm, when engaged in the regular sum of everyday activities, is between 1 and 60 per million[6], however, in an Ebola vaccine safety study the risk could be much greater. This does not necessarily mean that a high level of risk could not be justified by some other means, however.

The risks which a child in West Africa is exposed to in the sum of their everyday activities is very likely to be different to that of child in Australia. In Liberia and Sierra Leone, for instance, infant and childhood mortality rates are orders of magnitude greater than that in Australia[7]. This could be a stronger basis on which to justify exposing children to a significant risk. For the terminally or severely ill child who participates in risky therapeutic research, the relative risk of the research is less than that for a healthy individual. Even though level of risk is the same, the terminally or severely ill child is exposed to relatively lower level of risk than the healthy child due to the differences in their unchangeable circumstances. Put differently, the research exposes the ill child to levels which we would otherwise not accept (on the basis of a potential direct benefit), but we must accept this level if we are to accept the facts of their situation, and the fact that we can mitigate their current risks by no better means. Likewise, a child in West Africa who is exposed to a greater level of everyday risk than a child elsewhere might find that the level of risk exposure in the nontherapeutic research is relatively insignificant despite being grossly significant relative to other everyday levels of risk for children elsewhere. This means that significantly risky nontherapeutic research could be relatively non-risky to children in West Africa, and thus justifiable on this account.

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[6] *Ibid 1.* p. 533.

[7] 'A Spatial Analysis of Childhood Mortality in West Africa' Deborah Balk, Thomas Pullum, Adam Storeygard, Fern Greenwell, Melissa Neuman. Population, *Space and Place*, 2004, v. 10, p. 176.

West African children would also have an interest in seeing the benefits of such research come to fruition, which can only happen by the research being conducted. In the case of the safety testing of an Ebola vaccine, if the tests showed the vaccine was safe and effective, humanitarian organisations would likely be confident in administering a public health program. Such a program would likely seek to vaccinate large portions of the at-risk population in West Africa, hopefully leading to the eradication of the virus or a significant slowing of its transmission. Being a part of these initial safety tests, then, would be potentially becoming a part of the public health successes that were to follow. However, even if the tests showed the vaccine was not completely safe for children, such a result would still be scientifically useful in the sense that it would tell us what *not* to do or who *not* to administer the vaccine to. Therefore, even in this instance, participating in the research would be directly helping to avoid unsafe administration of the vaccine in certain segments of the population should a public health program still be pursued. And even if it wasn't, and the vaccine was altogether abandoned, we would have still learnt something scientifically, and again what *not* to do. These potential aversions of further disaster and trauma could be just as important as the pursuing of effective treatments and vaccines. After all, we would not wish to make a desperate situation even more so.

Science and public health are also long-term endeavours, with long-term goals. As such, children who participated in nontherapeutic research now could find that they directly benefit at some later point (on top of the indirect benefits of scientific advancement and the betterment of public health). For example, it could be that these children then go on to have children of their own who would benefit from the existence of an Ebola vaccine and the scientific knowledge that went along with it. The benefit needn't be claimed in some faraway time, however; it could simply be that by participating in the safety trial that that child's siblings, age peers, and the child themself would directly benefit vis-à-vis living in a community that what would acquire herd immunity from a disease it would have otherwise continued to suffer from.

Given that children in West Africa participating in this research might find it relatively non-risky compared to their everyday level of risk exposure, and that they would likely benefit indirectly and perhaps directly from the results of the research, the only other major hurdle for their ethical recruitment is that of lacking the capacity for fully-informed consent. That we so happen to need children for the research doesn't seem like enough justification in and of itself to warrant ignoring this potential lack of capacity for informed consent. And to rely solely on something like the US Common Rule, which only requires assent of the child and proxy informed consent from parents or guardians, might be inappropriate when the gross risks are so significant (even if relatively insignificant to the child). Additionally, the US Common Rule does not normally provide for risky nontherapeutic research such as this, unless approved by a special committee. Thus, a more rigorous form of consent is required - one that can better overcome our concerns about informed consent. But how will we achieve this? Well, perhaps we have been underselling the capacities of children for consent, as well as underselling adults' capacities to reliably make decisions on behalf of children which are generally in their best interests. After all, does a 17-year-old really, on her 18th birthday, suddenly become so much more mature that her consent should be classed as fully-informed one day and impossibly so the day before? No, her ability to be informed and make her own decisions will develop gradually, like for all children and adolescents. To seek to arbitrarily deny otherwise mature, informed adolescents who just so happen to have not yet reached their eighteenth birthday seems not only unempirical but also unjust. For, if we seek to deny her consent's proper status, we have (in an ironic attempt at 'protecting') actually subverted her autonomy and interests, which might also be the case for even younger adolescents and children. Who is to say that children, after all, could never genuinely understand and give a level of consent which is sufficiently informed (or, at least, not informed to a lesser degree than that of the average adult)? Answering such a question might lead us to wonder about how many grains of sand must be removed before the pile is no longer a heap (or how many months or years can be taken away before consent can no longer be

'informed' to a level which satisfies our ethical principles, especially of autonomy and protecting children from undue harm that they cannot foresee due to their limited capacities).

In these greyer areas, we must turn to the adults in these situations for assistance. While, like in the US Common Rule, parents should give proxy informed consent, that itself is not enough - given the stakes, they should also seek (in collaboration with other adults, for example the involved medical or research team) to ensure their child's consent is suitably informed. For, if an adult was attempting to give consent in the adults' arm of the safety study based on a set of irrational beliefs (that they would be cured of some unrelated disease by participating in the study, for example), we would rightly seek to correct this irrational belief as it does not support or respect the participant's autonomy[8]. If this irrational belief could not be dismissed by the participant, then we might seek to remove them from the study, since we could argue that their consent wasn't properly informed. We could then recruit a new adult participant who did not hold this irrational belief, and therefore could give fully-informed consent. A very similar scenario could play out for the children's arm of the safety study. We could, for every potential child participant, seek to ensure that they were not holding irrational beliefs about the nature of the study or other relevant facts. We could also repeat this process for any number of required elements of what we decided to define as our standard for suitably informed consent. We might say that for the child's consent to be informed, they must be able to demonstrate to us that they are acting voluntarily and can accurately articulate the material risks, benefits, and nature of the study[9]. Such a system could only work, however, for children above

[8] 'Should informed consent be based on rational beliefs?' Julian Savulescu, Richard Momeyer. *Journal of Medical Ethics*. 1997 (23) p. 287.

[9] *Principles of Biomedical Ethics* (4e) Tom Beauchamp, James Childress. 1994, Oxford University Press, p. 156.

a certain age - not an arbitrary age, but an age at which they (as an individual) could properly comprehend our required elements of informed consent[10].

For children who did not yet have the capacity to comprehend these elements of informed consent, parents (again, in collaboration with other adults) could give proxy informed consent on behalf of the child, only this time accounting for the entire proportion of the consent. In these cases, however, there would need to be some additional justification as to why such young participants were needed (some forms of scientific or methodological necessity might provide enough reason, as an example), and why older participants - who had at least some capacity to consent - could not be recruited instead. In fact, as an overarching trend, the researchers ought to preference (where possible) the recruitment of participants who have the highest capacities for informed consent or some level thereof. Where this is not possible, adults must make a determination of the child's interests as best they can. While we cannot guarantee that such determinations will always be perfectly accurate, we can generally assume that parents will seek to advocate in their child's best interests. Some may object to this, saying that you cannot know what is in the child's interests at all, or perhaps that because the child cannot understand their interests that they cannot yet have any. To this, I reply: while it can be difficult to know exactly what their temporal interests are (such as when they are crying), we do know that they have some undeniable general interests. We cannot say, for example, that it is not in the infant's interests to consume food and water, or to be warm and have general comforts and proper sleep. We know these interests exist because we are able to interpret their non-verbal behaviour. However, we can also attempt to make reasonable determinations about their future, long-term interests, which are far more likely to form the basis of a justification to involve them in the nontherapeutic research. As discussed earlier, their contribution to the study could lead to direct and indirect future benefits. What we might be

[10] ' Participation in biomedical research: The consent process as viewed by children, adolescents, young adults, and physicians' Elizabeth Susman, Lorah Dorn, John Fletcher. *Journal of Pediatrics*, 1992, v. 121 (4), p. 551.

understandably wary of, however, are selfish or unthinking parents who might enlist their child because they see it as a way of potentially gaining some of the direct and indirect benefits of the research, or because they do not care about what happens to the child or are not adequately concerned for their welfare. Such parents might be deterred, however, by responsible researchers.

Nevertheless, couldn't researchers attempt to aid selfish or unthinking parents in potentially not putting the interests of the child before their own or the study's? Or could some other iteration of an unethical researcher or slippery slope type argument occur? Possibly, and so this might be reason for us to insist on oversight measures in the conductance of such research projects. We might mandate that an independent reviewer or committee review cases in which a child has been unable to demonstrate sufficient competence to give informed consent. We might otherwise appoint an independent guardian whose role it is to act as if also a parent to the child, and who would have to be in agreement with the actual parent/s and research and medical staff for the child to participate. The independent guardian could also act as the parent (for the purposes of providing proxy informed consent) for orphaned children who lacked a close legal guardian due to foster or orphanage care but still wanted to contribute to the study. Such a case would be more likely to be an adolescent, as they would presumably have to proactively seek out the researchers and the study - that is, the researchers should not go *looking* for an especially vulnerable population: orphaned children. On the point of these vulnerable populations, and to help further avoid exploitation of children, the researchers should also not seek to overly compensate the research participants or their families, as this may inspire impure motives in parents.

It would seem that, in the case of a significantly risky Ebola vaccine needing to be tested on children for nontherapeutic purposes, there could be an ethical case made which involved child participants in West Africa. What about other cases, though? Could we apply some of the principles outlined so far to make clear judgements about their ethical status?

Could we imagine another version of the Ebola vaccine safety study on children which would be ethical outside of West Africa? The main problem is that children outside of West Africa are unlikely to benefit as greatly due to Ebola not directly affecting their community. That said, perhaps, for particularly mature adolescents who could provide informed consent practically indistinguishable from an adult's, we could allow them to participate in the study based on altruistic motives. If this was our justification, the child/adolescent would need to be significantly older to account for the large jump in relative risk due to stark geographical and socioeconomic differences, as well as the fact that there is almost no chance of there being major direct or indirect benefits for the child/adolescent. A problem that might then arise, however, is in terms of generalisability since the way children of different ages metabolise and respond to drugs and vaccines can be different.

A different case could be one in which children were being recruited to donate stem cells to research project aimed at developing a new treatment for a common group of adult disease-suffers. Here, the therapeutic benefit is not immediately to themselves but to others. However, like for the children in West Africa, they could directly benefit (and even receive a therapeutic benefit) at a later time in their lives if they were to eventually develop the disease. If not them, then it could be someone they know or are close to. Donating stem cells, however, is quite a low-risk procedure[11], but - in principle - it could be justifiable to allow participation in a similar project with greater risks.

Not all cases can be justifiable, however. If there was no expected or likely direct or indirect benefit for the child at the time of the nontherapeutic research or at some time in the future, and if there was additionally no possibility of a relatively high standard of informed consent, it would almost certainly be unjustifiable to expose children to gross significant risks. This would likely still be the case even if the children's everyday level of risk was quite high and the gross significant risks therefore relatively low or moderate. That is to say that the gross level of risk always matters, no matter the local context. This is because while we can do almost nothing for the terminally ill child

[11] 'Children as Hematopoietic Stem Cell Donors' American Academy of Pediatrics Committee on Bioethics. *Pediatrics*, 2010, v. 125 (2), p. 401.

and therefore not change their everyday level of risk exposure, there are systemic issues which we might have minor (but still some) influence over that help cause great everyday level of risk exposure in places like Liberia and Sierra Leone. Although none of us could reasonably, actively support such high levels of risk exposure, we effectively help (in whatever small way) perpetuate them if we refuse to acknowledge that everyday gross risk for children could theoretically be much lower, as it is in places like Australia, and that therefore this gross level of risk matters. In practice this means that the local level of risk exposure cannot be used as an excuse to increase the level of risk which children would be exposed to in already grossly risky nontherapeutic research. For the same reasons, nor would it be justifiable for researchers to fail to reduce the level of risk involved in the research if such a reduction would not cause scientific or methodological deficiencies. Researchers therefore have a moral responsibility to at all times seek to limit the gross amount of risk which will subjects and participants will be exposed to in any given study, no matter the local context.

Parents and guardians also have responsibilities, mainly to their children, but also to the researchers. For their children, they must seek to ensure that the child is as informed as their capacity allows them to be and that their ultimate decision (to participate or not participate) is truly their own decision and aligns with their best interests (to best of everyone's estimation). For their interactions with researchers, parent and guardians ought to be attentive and helpful in the collaborative effort to gain the best possible informed consent for the child, which could include obtaining independent advice (especially medical advice) on the suitability of the study to the child. Children also have a similar set of responsibilities. They should seek to engage with their parents/guardians and the research staff in the informed consent process as best they can, including in the communication of their personal values (if they are able to be identified). Children (like adults) may also have some weaker obligations to participate in altruistic nontherapeutic research if suitable participants cannot be recruited from elsewhere who would not be exposing themselves to a lesser magnitude of risk (and also assuming that they themselves are well suited to the study - for

instance, they should not assume risks that they believe would likely lead to emotional or psychological trauma by means of the high level of risk exposure alone, and not necessarily even the potential realisation of those risks). This leads to the final and most significant obligation, which is that all suitable people have an obligation to have a basic preparedness to contribute to our societies and advance our community's interests, even when such a contribution exposes us to a significant or unknown level of risk. This therefore includes participating in potentially significantly risky nontherapeutic research if we are able and willing to so. Without such participation, we effectively force others to take these risks for us, or we collectively condemn each other to a society in which we cannot hope to regularly halt or cure dangerous diseases. Although such participation possesses a greater danger for children (predominately due to issues discussed here regarding informed consent) than it does adults, children are still needed for significantly risky nontherapeutic research due to the fact that diseases effect both adults and children. Further, some effects that diseases have on children are or can be different to how they affect adults, for example, in Addison's disease and some psychiatric disorders (which can sometimes be classes similarly by symptom constellation but are totally different in aetiology).

The principles which can justify significantly risky nontherapeutic research on children are a combination of: (1) direct or indirect benefits to the child participants now and/or in the future (and these benefits need not necessarily be medical, they can also be socioeconomic or otherwise non-medical); (2) a high standard of informed consent that fundamentally focuses on the child participant's understanding (and capacity for understanding) of relevant features of informed consent. Researchers, parents and guardians, as well as child participants themselves, have different roles and obligations towards one another. This is not an issue of seeking to find excuses to expose children to risk, but rather an issue of seeking the least risky and most ethical way to do so if and when required by public health emergencies or to achieve directly beneficial scientific breakthroughs.