BELGIAN ADVISORY COMMITTEE ON
Bioethics

Opinion by letter No 19 on reporting incidental findings during exploratory research in the development of thoracic CT population screening for lung cancer in a high risk population

Request for opinion dated 19 August 2024 from the University of Antwerp

Admissibility of the request: Committee plenary session of 14 October 2024
Adoption of the opinion by letter: Committee plenary session of 9 December 2024

Preliminary Warning:
The committee's opinions are drafted in Dutch and French. Please consider these two language versions as official, even if translations in other languages are available.

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BELGIAN ADVISORY COMMITTEE ON
Bioethics

18/12/2024

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your reference
your letter of 19 August 2024

Subject: Your request for guidance on reporting incidental findings during exploratory research in the development of thoracic CT population screening for lung cancer in a high-risk population

Dear Ms. Snoeckx,

In your e-mail dated 19 August, you asked us the following question on behalf of the University of Antwerp regarding the ZorALCS study, a feasibility study aimed at a population-based lung cancer screening programme:

> *Is it ethically responsible not to mention, or to take no further action regarding, incidental findings in low-dose CT thorax looking for lung cancer in a high-risk group of individuals selected in a population-based study, assuming that during the process of shared/informed decision making and after reviewing the informed consent document and signing it for approval, the screened person is aware of it*?

The Committee wishes to respond to the request for an opinion in the form of the present letter opinion.

* * *

1. Notes on terminology

Whether it is routine medical research prescribed by the patient's physician or research conducted on participants for research purposes, it is not uncommon in modern high-tech medicine for 'abnormalities' to be detected. These abnormalities only qualify as *incidentalomas* or incidental findings **when they are discovered during a medical examination for other purposes.**

With the increasing use of more advanced radiology and imaging techniques, identifying incidentalomas or incidental findings has become a common occurrence. Some authors even find it more appropriate to refer to secondary findings rather than incidental findings. Apart from these terminological aspects, it is important to emphasise the significant development of ethical recommendations in recent years regarding the management of incidental or secondary findings (depending on the terminology used) in the specific context of research. This is a different context to that found in the healthcare sector, both in terms of the objectives pursued and the applicable ethical guidelines.

2. *Distinction between the research framework and the care framework*

The distinction between care and research was clarified by the Belmont Report in 1979.

> *It is important to distinguish between biomedical and behavioural research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research.* ***The distinction between research and practice is blurred partly because both often occur together*** *(as in research designed to evaluate a therapy) (...).* ***For the most part, the term "practice" refers to interventions that are designed solely to enhance the wellbeing of an individual patient or client and that have a reasonable expectation of success.*** *The purpose of medical or behavioural practice is to provide diagnosis, preventive treatment or therapy to particular individuals [...].* ***By contrast, the term "research' designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships).*** *Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.*[1]

The essential criterion for **qualifying**[2] whether a given situation falls within the context of care or research is that of the purpose of the proposed intervention. This distinction is of course not intended to deny the close links between the domains of research and care, which are particularly evident in the context of a study such as the one you are planning, intended precisely to prepare actions in the area of public health.

The importance of this distinction and the consequences of applying it ethical reflections in the second half of the 20th century were significant, both for research participants and patients:

- For research participants, this distinction made it possible to introduce a range of safeguards that now provide them with a degree of protection at least equivalent[3] to

[1] Emphasis added. The Belmont Report
[2] The term must be understood in its technical and legal meaning.
[3] If not higher, given that participants (especially healthy volunteers) do not directly benefit from research or have any guarantee that they will, given that the purpose of research is primarily to produce insights that can be extended to benefit the community.

that enjoyed by patients under medical ethics and the regulations applicable to healthcare.

- For patients, it has made it possible to eliminate any confusion there may be in certain cases between what is required for care and interventions performed for experimental purposes by their physician. As such, it is essential to clearly inform them and ask specific consent for the study.

Finally, this distinction has directly contributed to the development of research ethics committees, which have become the monitoring mechanism of choice within research.

Qualifying the situation presented as "research" implies that the research ethics committees are responsible for assessing it under the applicable law[4], and that the assessment must be carried out in light of the relevant framework and principles, namely the principles related to research ethics.

3. The reporting of incidental health results

3.1. **In the context of care**: the principle of the right to quality service provision that meets the needs and preferences of the patient.

In the context of care, all incidental findings are communicated to the patient by the healthcare practitioner. This is in the context of a conversation in which all possible treatments must be considered in light of the patient's "current and future care preferences[5]."

Only the patient's express refusal to be informed of their health results may be grounds for the professional not to communicate them, provided that failure to do so would not result in clear and serious harm to the health of the patient or third parties. If this is the case, the healthcare practitioner must consult with another healthcare practitioner and also discuss with the confidant before communicating the relevant results[6].

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[4] Law of 7 May 2004 on experiments performed on human subjects. *B.O.G.*, 18.05.2004 https://etaamb.openjustice.be/nl/wet-van-07-mei-2004_n2004022376

[5] Art 7, §2 of the law of 22 August 2002 on patients' rights *B.O.G., 26-09-2002. Article 5 of the same law specifies the following (freely translated):*
"The patient, without any distinction on any ground, has a right, vis-à-vis the [healthcare practitioner], to quality service that meets their needs.
The healthcare practitioner respects the human dignity and self-determination of the patient and takes into account the patient's goals and values. Where appropriate, the healthcare practitioner organises early care planning to this end."

[6] *Ibid.* art 7, §3

Other than a patient's refusal to be informed of their health results, are there situations in which a healthcare practitioner can withhold information from a patient regarding incidental results discovered during medical testing? The Law on Patients' Rights, which aims to promote quality information and respectful, "horizontal" relationships between patients and healthcare providers, limits the possibility of withholding information to cases where "the healthcare practitioner believes that providing all information would manifestly cause serious harm to the patient's health[7]." In such cases, the healthcare practitioner should consider "whether the information in question can be communicated gradually[8]".

For example, the Law on Patients' Rights states as a general principle that patients must be given all information regarding their health. Exceptions are only possible based on the patient's wishes (in this case, their express refusal to be informed) or to protect them from even more serious harm, in which case specific precautions must be taken.

3.2. **In the context of research**: the principle that the health needs of participants must be taken into account

Ethical guidelines for research have clearly evolved **toward better protection of research participants, including more of a focus on their health needs. It should be noted that this increased focus on, and protection of, the health and well-being of participants is not limited to the pathologies examined in the study. This focus also extends to conditions outside the context of the research, once they are discovered during the research. This is the case even when these conditions result from structural situations that are not the responsibility of the researchers (e.g., malnutrition or poverty-related conditions).**

For example, Guideline 6 "Caring for Participants' Health Needs" of the CIOMS Guidelines[9] (2016) states that:

> ***It is generally inappropriate to require researchers or sponsors to take on the role of a country's health systems. Nevertheless, research with humans often involves interactions that enable researchers to detect or diagnose health problems during recruitment and the conduct of research.*** *Similarly, clinical research often involves*

[7] *Idem.*
[8] *Ibid.* art 7, §4
[9] International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016. https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

care and preventive measures in addition to the experimental interventions. In some cases, participants may continue to need the care or prevention provided during the research after their participation in the study has ended. This may include access to an investigational intervention that has demonstrated significant benefit. ***In all these situations, researchers and sponsors must show care and concern for the health and welfare of study participants.*** *This is justified* ***by the principle of beneficence,*** *which requires researchers and sponsors to safeguard the health of participants when it is in their power to do so. It is also supported* ***by the principle of reciprocity;*** *participants assist researchers in generating valuable data and, in return, researchers should ensure that participants receive needed care or preventive measures to safeguard their health.* ***Importantly, the obligation to care for participants' health needs is not limited to research in countries with limited resources (see Guideline 2 - Research conducted in low-resource settings) but is a universal ethical requirement in research. Furthermore, even though the provision of care during and after the trial may be an incentive for people in low-resource settings to enrol, it should not be considered an undue influence.***

Ancillary care. *Sponsors are, in general, not obliged to finance interventions or to provide health-care services beyond that which is necessary for the safe and ethical conduct of research. Nevertheless, when prospective participants cannot be enrolled in a study because they do not meet the inclusion criteria, or enrolled participants are found to have diseases unrelated to the research, researchers should advise them to obtain or refer them for medical care (...).*[10]"

As such, **from an ethical perspective, it is no longer widely accepted that research teams, due to the research context (as opposed to the care context), do not consider it necessary to inform participants of certain information that could potentially have a direct or indirect impact on their health, in the short, medium or long term. Research teams must therefore determine the best approach to consider the health needs of participants.**

This ethical requirement can in some cases entail a significant financial and logistical burden for research teams. For example, it is not uncommon for additional expertise not required by the original research question to be relied upon in order to expertly reinterpret certain images that reveal an incidentaloma. In addition, certain samples may need to be sent to a

[10] International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS); 2016. WEB-CIOMS-EthicalGuidelines.pdf

laboratory to have biological results, which were initially obtained in research laboratories without accreditation for reporting clinical biological results, verified and validated.
In all cases, careful consideration must be given in advance to the best way to consider the health needs of participants, while at the same time keeping open the possibility of research, whose expected benefits are for the community as a whole (but can never be guaranteed).

The potential tension between these different objectives: the feasibility of the research on the one hand and taking into account the health needs of the participants on the other, may be all the greater when, on the one hand, the research results are expected in a context of public health, and on the other hand, the incidental findings pertain to pathologies that have a potentially significant impact on the health of the participants. It is crucial to strike a balance, in consultation with the research ethics committee responsible for reviewing the protocol and ethical safeguards for participants. Regardless of the intensity of the tension between these objectives, it is still vital to respect the Helsinki Declaration:

> *"The primary purpose of medical research involving human participants is to generate knowledge to understand the causes, development and effects of diseases; improve preventive, diagnostic and therapeutic interventions; and ultimately to advance individual and public health.*
>
> ***These purposes can never take precedence over the rights and interests of individual research participants.***[11]**"**

As explained above, the fundamental ethical principles underlying the obligation to consider the health needs of participants are the principles of beneficence and reciprocity. It is important to emphasise that these principles must be combined with the principle of autonomy: participants must be able to express, with full knowledge of the facts, any preference "not to know."
Participants must therefore be informed in advance of the possibility of incidental findings in the context of the interventions required for the study. This information must be provided as **part of the information provided prior to inclusion.** It is recommended that participants be explicitly asked **whether or not they want to be informed about these results. This**

[11] Emphasis added. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Participants, Helsinki, Finland, 2024 (final revision).
WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants – WMA – The World Medical Association

approach is generally appreciated and strengthens confidence in research[12]. Again out of respect for the autonomy of the participant, the "right not to know" can never be assumed.

4. Incidental findings obtained in a research framework: what should be communicated, and how?

4.1. What should be communicated?

While it is no longer ethically conceivable for the research team to, a priori, decline any responsibility for incidental findings, it is still complex to decide what results should be reported to the participant (unless the participant has explicitly indicated that he or she does not want to know) and according to what modalities.

A poorly designed reporting process risks situations of overdiagnosis and overtreatment, as not all findings are necessarily clinically relevant. This can cause a lot of concern and lead to unnecessary follow-up tests and treatments, with all the associated risks and costs. Moreover, large-scale reporting can overburden the healthcare system.
Assessing these various parameters is complex, and although there are a variety of different views in the professional literature, a generally accepted criterion is that of the *best medical interest* of the participant:

[12] Walpert AR, Dunderdale C, Srinivasa S, Looby SE. Participant perspectives on management and communication of incidental findings identified on radiographic imaging performed during a clinical research trial: A single site pilot study. Contemp Clin Trials Commun. 2024 May 16;39:101305. doi: 10.1016/j.conctc.2024.101305. PMID: 38798946; PMCID: PMC11127463.
Hegedüs, P., von Stackelberg, O., Neumann, C. et al. How to report incidental findings from population whole-body MRI: view of participants of the German National Cohort. Eur Radiol 29, 5873-5878 (2019). https://doi.org/10.1007/s00330-019-06077-z

> "While recommendations as to what incidental findings can and should be disclosed vary, there is a common thread, supported by a number of commentators, that could be described as the **best-medical-interests standard**. This standard tasks researchers with evaluating a given incidental finding along roughly three criteria: validity, significance to health (and sometimes reproduction), and clinical actionability. Validity refers to the accuracy and reliability of the finding; a mere suspicion of a problem would not merit reporting, but a finding informed by a number of clinical studies might. Significance to health and reproduction refers to whether the finding could have a substantial impact on someone's health or (via reproduction) that or his or her offspring. A life-threatening brain tumour clearly passes this test, and a genetic variant related to earwax viscosity would not. And finally, clinical actionability refers to the potential for a clinical intervention to alleviate the health issue (or, perhaps, the possibility for the finding to alter reproductive decision-making). Predispositions for treatable conditions like breast cancer would pass this test, while misattributed paternity likely would not (unless there was some expected medical intervention where paternity would be relevant)" . [13]

This best medical interest of the participant requires three parameters (also known as the ACA criteria) to be taken into account:

- The accuracy and confidence that can be accorded to the result obtained (*accuracy - A*)
- The impact and risk of the detected abnormality for the participant (*clinical significance - C)*
- The available medical resources to treat the detected abnormality and ensure appropriate follow-up and/or treatment. (*actionability - A)*

Any parameter that is part of the standard of best medical interest of the participant may require the research team to rely on specific expertise or additional resources where possible. This may include, for example, reproducing results by an accredited laboratory or consulting appropriate professionals to assess current and future options for therapeutic

[13] G. Owen Schaefer and Julian Savulescu, "The Right to Know: A Revised Standard for Reporting Incidental Findings," *Hastings Center Report* 48, no. 2 (2018): 22-32. DOI: 10.1002/hast.836. It should be noted that these authors believe that the standard of best medical interest for the patient is not enough and that in certain conditions they advocate disclosing information that does not primarily fall under this standard but may contribute to serving the 'interests' of the participant.

follow-up. Nevertheless, the transition between the research and care context is usually ensured through an established procedure that makes it possible to refer to the patient's GP.

4.2. How to communicate? The challenge of the transition between research and care.

It is crucial that a result which is important to the patient's health can be communicated **without delay** and **expertly** by **a healthcare provider familiar with dealing with patients.** That is why it is usually recommended that, after being informed by the research team, the GP communicates with the patient and discusses the most appropriate treatment.

In practical terms, the relevant participants can be invited by letter to contact their GP, who has also been given the relevant information. This dual communication (to the participant and to the physician) is based on the participant's prior consent during the information and consent process, whereby the specific needs of the participants are respected on the one hand, and the confidentiality of medical information is respected on the other.

In the context of European countries where access to healthcare is relatively secure and social security provides a solidarity mechanism, the research team is generally not expected to fund the care or take responsibility for the care pathway.

5. Conclusions

Detecting incidental findings during research has been the subject of extensive discussion in the professional literature. The current framework for research ethics recommends **taking participants' health needs into account**, even if these needs are not related to the pathology or medical research question.
The ethical principles underlying this decision to consider the health needs of participants are the **principles of beneficence** (and do no harm) and **reciprocity**. However, these principles must be balanced against the key principle of **the autonomy of the participant**, who must be able to express their "right not to know," which must be respected. In order for the participant to be able to make an informed choice as to whether or not to be informed, it is essential that they be informed **in advance**, at the time they are included in the research, of the possibility that incidental findings may be made in the context of the study, and that they were able to express their views accordingly.

The criterion of the participant's **best medical interest** should guide research teams in making the transition between the context of research and that of care. Teams are often not equipped to deliver the results themselves, let alone to ensure that they are managed according to the nature of the results and the needs and preferences of the participant. It is therefore imperative that the participant be referred to a competent healthcare practitioner who can consult with him or her regarding setting up (or modifying) his or her care. It must be possible for this referral system to be activated without delay, which means that it has to be planned in advance, also taking into account the specific needs of certain categories of participants and their possible difficulties in accessing care[14].

Aware of the complexity and burden of defining such a process, the Committee invites research teams to carefully prepare in advance the procedure for managing the incidental findings that may come to light during the research. The Committee also recommends entering into a qualitative dialogue with the research ethics committee(s) responsible for approving the research in question.
In summary, the decision whether or not to communicate incidental findings is complex and requires careful evaluation of the ethical, medical and practical dimensions. A transparent and well-informed policy, focused on the health needs of participants, is crucial to protect both the interests of participants and society.

Sincerely,

Patrick Cras,
President of the Advisory Committee on Bioethics

This letter opinion was jointly drafted by Virginie Pirard, Vice President.

[14] In this regard, refer also to: Vander Wyst KB, Olson ML, Bailey SS, Valencia AM, Peña A, Miller J, Shub M, Seabrooke L, Pimentel J, Olsen K, Rosenberg RB, Shaibi GQ. Communicating incidental and reportable findings from research MRIs: considering factors beyond the findings in an underrepresented pediatric population. BMC Med Res Methodol. 2021 Dec 5;21(1):275. doi: 10.1186/s12874-021-01459-8. PMID: 34865631; PMCID: PMC8647358.