

Incidental Findings – Understanding of Risks by Research Subjects and Implications for Research Ethics¹

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Abstract

This paper reports results from an empirical study of the effects of incidental findings on research subjects who took part in a whole-body MRI examination within a larger population-based study in Germany. Following a brief review of the background and methods for this study, important quantitative and qualitative results will be discussed. The findings of this study suggest that a) inordinate or disproportionate stress is not observed in the vast majority of research subjects receiving incidental findings, despite assumptions to the contrary. However, an important caveat from the point of view of research ethics is that b) reactive stress, where it does occur, can be reduced by various measures, e.g. by modification of the approach to reporting findings and that c) approaches to informing research subjects of incidental findings from this type of study should be improved so that the research subjects can evaluate the validity of whole-body MRI results more realistically.

Keywords: Incidental findings, Whole body MRI, Population based medical research,

¹ This publication was written in the course of the research association Greifswald Approach to Individualized Medicine (GANI_MED). The GANI_MED project is financed by the German Federal Ministry of Education and Research and the government of the Federal State of Mecklenburg-Vorpommern (support code 03IS2061A). The Study of Health in Pomerania (SHIP) is part of the research network Community Medicine at Greifswald University. The research network is supported by the German Ministry of Education and Research, the Ministry of Education and the Arts and the Ministry of Social Affairs in Mecklenburg-Vorpommern (cf. <http://ship.community-medicine.de>). The MRI imaging within SHIP is financed by Siemens Healthcare (Erlangen, Germany) and Mecklenburg-Vorpommern. Greifswald University is a member of the Interchange program of the Center of Knowledge of the Siemens AG. This paper is the English version of an article which was published elsewhere previously (Steger, F. (ed.), *Medizin und Technik. Risikobewusstsein und ethische Verantwortung infolge technologischen Fortschritts*. Paderborn, 2012 (in press).

Background

A team at the chair of Systematic Theology at the Faculty of Theology at the Ernst-Moritz-Arndt-University of Greifswald has served as integral part of a project named GANI_MED (Greifswald Approach to Individualized Medicine) since October 2009, with Prof. Dr. Heinrich Assel serving as the head of the collaborating team. The overarching aim of GANI_MED is to establish a program in predictive Individualized Medicine at the university hospital. “Individualized Medicine” is taken in this project to be a combination of approaches and methods intended to improve medical prediction. These approaches would involve the integration of a range of clinically relevant parameters into clinical care in order to predict individuals’ risk for developing certain diseases or to predict the future course of pre-existing conditions. Moreover, these approaches would ideally predict the success of therapies with a high degree of specificity and sensitivity.²

The team at the chair of Systematic Theology has addressed a number of research ethics questions within GANI_MED, with a focus on two sub-projects:

1. The first sub-project aims at assuring that within GANI_MED the informed consent (IC) process and all related processes (data storage, data usage, biobanking etc.) are carried out according to legal and data protection standards, as well as standards of research ethics. This also includes creating the documents and informational pamphlets that are utilized in the IC process, cooperation on the design of data protection approaches and biobanks, current training for staff involved in patient information, and the development and implementation of recommendations regarding the practical arrangement of ethically sensitive processes within GANI_MED.
2. The other sub-project uses the methods of empirical social science in order to examine the effects of reporting incidental findings³ on participants in medical research, with the SHIP study (Study of Health in Pomerania)⁴ serving as the primary example. SHIP is a population-based study also established at Greifswald University. This manuscript focuses on the special issues pertinent to whole-body MRI performed as a part of this study.

The SHIP study was examined as a case study to help identify the issues relevant to returning incidental findings that could arise in GANI_MED. MRI examinations were planned for specific GANI_MED cohorts outside of clinical routine. Therefore, it was quite clear that the

² For aims, concept and structure of GANI_MED cf. Langanke et al. *Gesundheitsökonomische Forschung*, pp. 105-121 and Langanke et al. *Different Approaches*, pp. 440-441. The term of biomarker relevant for GANI_MED is explained in Langanke/Fischer. *Gesundheitsmanagement*, pp. 142-143. For the general debate about Individualized or Personalized Medicine cf. Golubnitschja, *Predictive Diagnostics* and Niederlag et al. *Personalisierte Medizin*. A very good overview of the different varieties and approaches is provided in Hüsing et al. *Individualisierte Medizin*.

³ A very good introduction to the current international discussion about incidental findings within non-clinical research is given by Hoffmann/Schmücker, *Ethische Problematik*. Furthermore, they adjust the term “incidental finding” as the presented paper does: An incidental finding is a non-intended finding which is the result of a study with research subjects and has an effect on the health or reproduction of the people concerned. Cf. Hoffmann/Schmücker. *Ethische Problematik*, p. 3.

⁴ For the cohort profile within SHIP cf. Völzke et al. *Cohort Profile*.

risk of incidental findings and – connected with this – questions about the appropriate methods for reporting these incidental findings would be raised in GANI_MED. The purpose of carrying out an empirical study of the MRI component of the SHIP study was to identify *best practices* relevant to the protection of research subjects and to guide quality improvement efforts as a part of GANI_MED. The SHIP whole-body MRI was a natural object of investigation because a) it served as a case study and reference for GANI_MED in discussions with the research ethics committee regarding the design of research processes, and b) it generated a relatively large number of incidental findings.

Method and Design

The study was primarily exploratory in nature, since there were almost no publications available about the effect of reporting incidental findings from whole-body MRI studies to research subjects. For this reason, no previously validated instruments were available relevant to this set of research questions.⁵ The exploratory character of this study is underlined by the order and choice of methods, especially its two-stage mixed-methods study design: For the first stage (quantitative) it was important to identify whether certain pre-empirical assumptions about expected stress are correct; thus we examined whether and to what extent certain *prima facie* expected stresses would arise. In the second stage (qualitative) we sought to clarify the details for those findings in the quantitative part that were unexpected or seemed counterintuitive, i.e. regarding those results which did *not* confirm or even refuted the pre-empirical expectations. In the course of this study, the advantages of this study's mixed-methods design became obvious.⁶

The quantitative portion of this study was based on two questionnaires while the qualitative portion was based on an interview. The first questionnaire was administered to all SHIP research subjects who underwent whole-body MRI in the period between March 3, 2010 and July 23, 2010. The questionnaire was administered to them in the period between the MRI examination and the following final consultation (n = 439, response rate = 96.5 %). The second questionnaire was mailed to participants. This timing for mailing the questionnaire was based on an algorithm that included, among other factors, whether the participant had received an incidental finding and, for those who did, whether four weeks had elapsed since that notification, in order to give them time to pursue further evaluation to clarify the finding. In total, the response was very high for the second questionnaire, as well (n = 409, response rate = 93.2 %). These values are especially striking given that this questionnaire was administered by mail!

At the beginning of the study the frequency of incidental findings was anticipated to be 30%.⁷In actuality, 152 out of 439 research subjects (34.6 %) received one. 134 of these

⁵ A survey by phone had previously been conducted in the summer of 2009. In this study, 20 research subjects who had participated in the whole-body MRI examination and received a report of incidental findings, were interviewed. This was the pilot phase for the development of a questionnaire designed by an interdisciplinary team (representatives of epidemiology, psychology, psychiatry, radiology and ethics). Cf. Schmidt et al. *Psychosocial consequences*.

⁶ For the advantages of integration of quantitative and qualitative methods cf. Kelle. *Integration*, pp. 227ff.

⁷ The number of incidental findings detected with imaging methods always depends, naturally, on the study protocol used for the examination, i.e. which body part is examined with which method. Wolf et al.

152 research subjects responded to the postal questionnaire. Four research subjects out of this group reported that they did not receive a written report of findings. However, one of them answered the relevant questions, though incomplete. It is not clear why another four research subjects, who said that they got a report of findings, did not answer the questions *within* the relevant section despite the fact that they completed the rest of the questionnaire. Overall, in the following analysis we will refer to these 131 questionnaires when speaking of the group “with incidental findings”.

14 research subjects said, surprisingly, that they received a report about a finding despite the fact that this was not the case according to the staff responsible for mailing the written reports within SHIP. Perhaps these statements by the research subjects referred to the final consultation or the oral report of a finding at the end of the MRI examination. The answers of these particular questionnaires were not used for the analysis because they could not be connected to any written report of findings.

Interviews were scheduled with 24 research subjects. These participants were chosen based on their answers to questionnaire items. For instance, some were selected because they reported high stress or dissatisfaction, or because at least one response in the second questionnaire differed significantly from their response to that same item in the first questionnaire. The first three interviews (B1 – B3) were needed in order to improve the approach and discussion guide, and were thus not used in the analysis. In addition, interview B17 could not be used because it was not properly recorded. In total, 20 interviews were analyzed. Every interview was divided into two parts: the first part was conducted methodologically as a *narrative interview*⁸, i.e. the person was asked an *initial question*⁹ in which he or she was asked to tell everything that came into mind regarding the whole-body MRI examination, from the invitation to participate up to the report of findings. The second portion of the interview was semi-structured. This portion of the interview followed a discussion guide designed not to influence the course of conversation too much while assuring that all relevant areas were addressed in the interview.¹⁰

The questionnaires were analyzed using SPSS (PASW Statistics 18), while the interviews were analyzed with the assistance of the software MAXQDA (10).

Clarification, diagnostics and report of findings within the SHIP MRI study¹¹

The capability for whole-body MRI has existed since July 2008. First, the head and body are examined, taking approximately 70 minutes. Second, additional examinations of the heart and the vascular system are performed. For female research subjects, MRI examinations of the heart and breast are done.¹²

Managing Incidental Findings, p. 221 reports that the number of incidental findings in examinations of the brain is, for instance, between 13 % and 84 % (sic!).

⁸ For narrative interview cf. Flick. *Qualitative Sozialforschung*, pp. 147ff.

⁹ Flick. *Qualitative Sozialforschung*, p. 147.

¹⁰ For guideline interview cf. Bortz/Döring. *Forschungsmethoden*, p. 314.

¹¹ This paragraph follows the presentation by Langanke/Erdmann in *MRT als Studienuntersuchung*, pp. 202-209.

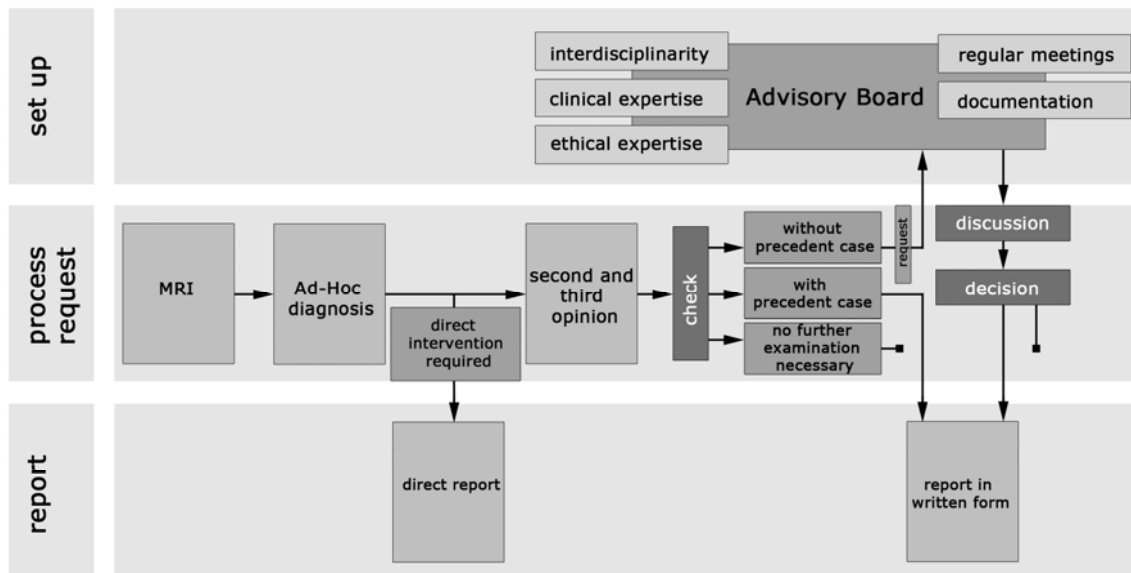
¹² cf. *SHIP Teilnehmerinformation*, p. 10.

Before undergoing whole-body MRI, every research subject must first participate in a multi-staged program focused on providing information and answering questions. This begins with the invitation to participate in SHIP (research subjects are selected at random) when each potential participant receives an extensive booklet about the aims and sub-parts of the SHIP study.¹³ Furthermore, persons arriving for an initial visit at the SHIP examination centre view a film. This film shows how an MRI takes place and describes the inconveniences (claustrophobia etc.) that are associated with participation in this examination. Directly before the examination, a personal consultation with medical study staff takes place. In this intensive 15-minute consultation the research subjects are informed “about the fact that it is possible that unanticipated results will be detected by the MRI which might need further clarification”¹⁴. On the other hand – according to the interim report – it is also assured that research subjects have understood the consequences of the MRI examination in case of a positive and/or unclear result which needs further clarification! Moreover, all research subjects were informed that the MRI examination is used for study purposes and *not* [highlighting in the original, P.E.] as a screening method.¹⁵

The information is given orally also with the emphasis that some findings, e.g. changes with unclear pathological value, will not be reported. If findings that need to be reported are detected, the research subjects will be contacted via mail within six to eight weeks.

The report of possible MRI findings within SHIP is performed through a specific procedure, of which the steps are shown in figure 1.

Fig. 1: Reporting of test results within SHIP



Directly after the MRI, a conversation with the participant takes place during which he or she

¹³ This is the printed brochure which is referred to as *SHIP Teilnehmerinformation* here.

¹⁴ Kühn. *Ganzkörper-MRT*, p. 3.

¹⁵ Ibid. *Italic in the original.*

can be informed about incidental findings which are acute and require immediately therapy. These findings are detected in the mode of an ad-hoc diagnosis. After this ad-hoc diagnosis, second and third opinions follow. In cases where the results are unclear, e.g. no precedent case exists, or differing opinions exist among reviewers, or in case of an apparent neoplasm, an interdisciplinary Advisory Board meets. Relevant findings are then forwarded to the research subjects in written form.¹⁶

It should be noted that clarification and diagnostics within SHIP are performed according to high standards. Great care is taken in both parts of the review process. This is demonstrated by an elaborate sequence of sub-processes and by, in case of an incidental finding that will be reported, a complex decision tree with various options. The establishment of an Advisory Board for the evaluation and processing of new, controversial, or particularly difficult cases should be positively highlighted here.

Results

This manuscript highlights some of the most important results from this study.¹⁷ Results are divided into quantitative results (4.1) and qualitative results (4.2), with a short interim summary following (4.3). Quantitative results are organized with regard to aspects of “stress”, “willingness to participate in future research” and “motivations for participation”.

Quantitative Portion

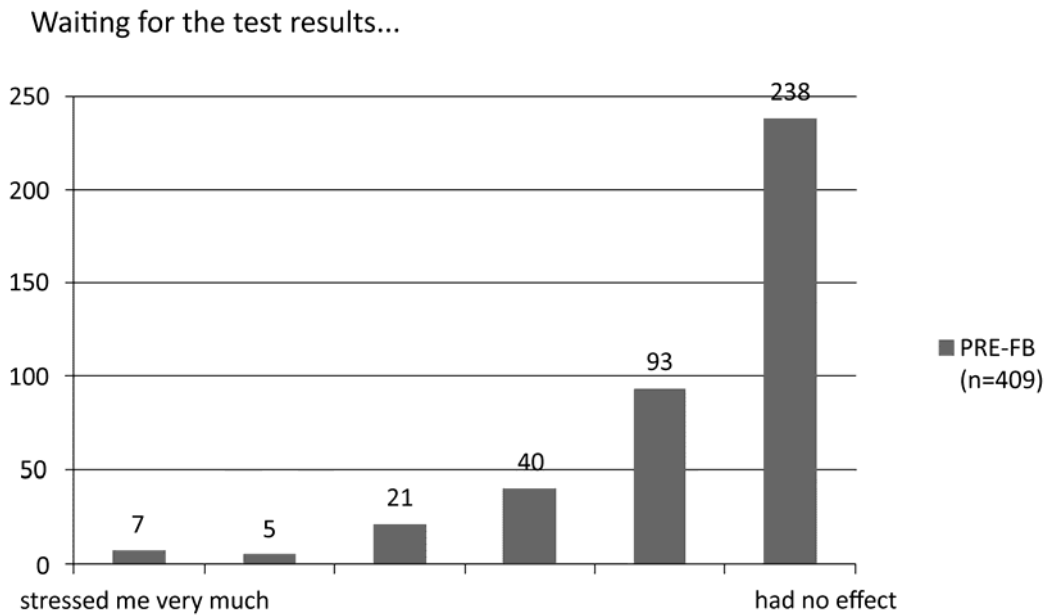
Stress

During the conception of this study, and again later during the development of empiric instruments, negative effects from the MRI examinations and the following report of findings were considered. A number of possible stresses were anticipated, including: a) waiting for the result, b) the result itself, and c) the consequences which arise from the finding. Given this early focus on stresses, responses on the second questionnaire were quite surprising. It became clear that the stress introduced by participation in this study was far less than estimated beforehand; waiting for the results was described as very stressful by only seven research subjects, five said that the waiting was quite stressful, and 21 research subjects reported it to be moderately stressful. The majority of the research subjects (91 %) reported that they felt little or almost no stress or effect caused by waiting for the result:

¹⁶ For detailed information about the diagnostics procedure cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, pp. 240ff.

¹⁷ Due to reasons of space, the results are limited here to the most important ones. The complete analysis of the data will soon be provided in a doctoral thesis.

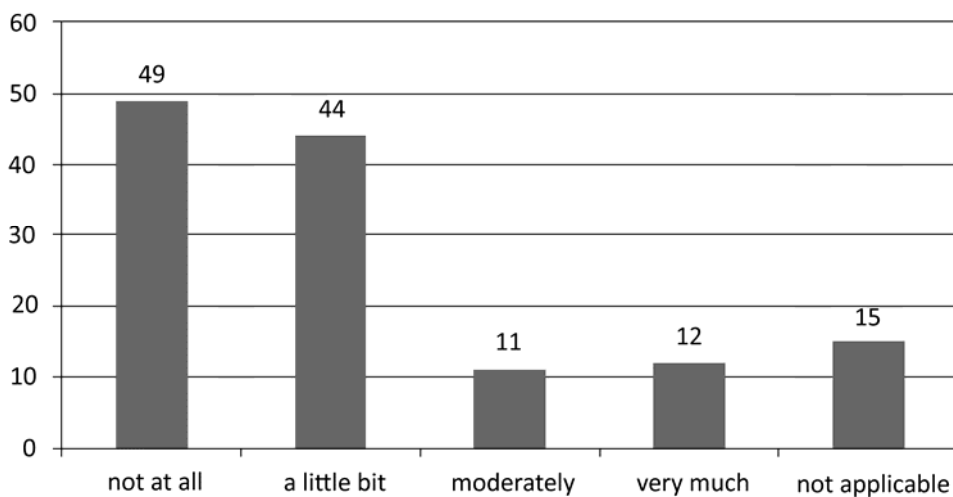
Fig. 2: Stress caused by waiting for the test results¹⁸



If one looks at the stress caused by the report of incidental findings for the 131 affected research subjects, 71% of them said that they were “not at all” or “a little bit” stressed. In contrast, 8.4 % felt “moderately” and 9.2 % “very much” stressed.

Fig. 3: Emotional stress because of reporting of the test results, n=131

Looking back, the reporting of the test results were emotionally stressing...



¹⁸ In this and the following figures, the missing values and responses which were recorded incorrectly by respondents are not displayed.

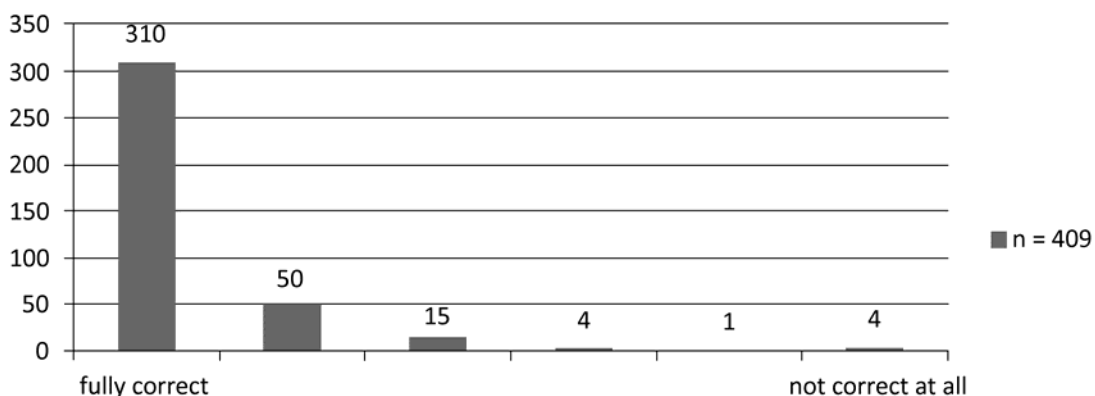
Having said this, it is clear that overall the stress caused by the report of incidental findings is relatively low. Despite this, it should be noted that when it comes to normative considerations, an effect in a small number of persons can be quite important.¹⁹ For this reason, it is important to differentiate the stresses that can be introduced by the report: some stress can be attributed to the result itself. This type of stress is inevitable, since unanticipated findings that have medical significance must still be reported. However, for certain stressful aspects of the report procedure, we must address to what extent that stress can be reduced. It should be considered here, for example, the stress that arises because the written report is not understood (“a little bit” 19%, “moderately” 8%, and “very much” 2%), or the stress caused by waiting for clarification of the finding (“a little bit” 29%, “moderately” 12% and “very much” 9%). Consequently, we want to evaluate the stress independent of its degree. In particular, we want to evaluate whether or under which conditions it would have been preventable, and whether research subjects need to face such stress in the future.

Retrospective evaluation of participation and willingness to participate again

Another assumption during the planning of this study was that some research subjects could be disappointed considering the discrepancy between the expected and the actual value of the MRI examination. Moreover this disappointment, so it was assumed, could have negative effects on the willingness to participate again. The questions at the end of the second questionnaire were focused on subjects’ satisfaction regarding their participation and their willingness to participate again. In this section as well the answers differed from those expected. The satisfaction of the research subjects was extraordinarily high as shown in the following chart:

Fig. 4: Satisfaction of the research subjects with the participation MRI examination

Looking back, I am satisfied to have participated in the MRI examination...



Very few participants were unwilling to participate again. The question “If I had been provided better information I would not have participated in the MRI examination” was answered by 28 research subjects with “yes” (6.8%), 351 research subjects said “no”

¹⁹ For the problem of the “ethical” significance of individual cases of the essentially *preventive* function of norms cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, p. 221.

(85.8 %) and 30 gave no answer or filled it in incorrectly (7.3 %).

In total, it can be assumed that less than 10 % of the research subjects were significantly stressed by waiting for the result and the result itself, whereas “customer satisfaction” and willingness to participate again was very high.

Motivation for participation

In these responses there was no indication that the study did not meet the expectations of research subjects. This can be explained in at least two ways. First, research subjects might have had appropriately low expectations for the benefits they would derive from the study. Any benefits they did receive, although small, thus met their expectations. On the other hand, research subjects might have had high expectations for the benefits they would receive, and interpreted any benefits as meeting these high expectations. In light of this, we examined the reasons research subjects voluntarily participated in the in the whole-body MRI examination. What kinds of expectations with respect to benefit were the most important in their decision to participate? Did research subjects realistically assess the risks of the participation?

Prior to participation in the SHIP whole-body MRI study, research subjects were informed of the following benefits:

- 1) They will be informed about acute life-threatening diseases in a consultation directly after the examination. In this case, transfer to the emergency department and/or admission to the hospital will be initiated.
- 2) Participants will receive a written report if an anomaly is detected which needs further examination. This anomaly could possibly be a life-threatening disease and could, if this is confirmed, require further therapy and medical supervision.
- 3) An explicit exception is that research subjects will not be informed about MRI findings related to the spine:

In the current state of medical knowledge it is not possible to accurately predict pathological conditions or complications from MRI findings. Therefore, from our point of view, the possible disadvantages which could arise from being informed of any finding definitely outweigh the predictive value of such a finding.²⁰

- 4) Furthermore, research subjects are informed that the “predictive value of the MRI examination is still unclear for many diseases”²¹. Also, the amount and quality of the images are chosen for research reasons so that false positive as well as false negative findings might occur.
- 5) Research subjects are informed that “the MRI examination is done for study purposes and *not* [highlighted in the original, P.E.] as a screening method”²². For the research subjects this means that they should continue to attend medical check-ups, despite their participation in the whole-body MRI. They should consult a doctor in case of unclear conditions which could indicate a serious illness.

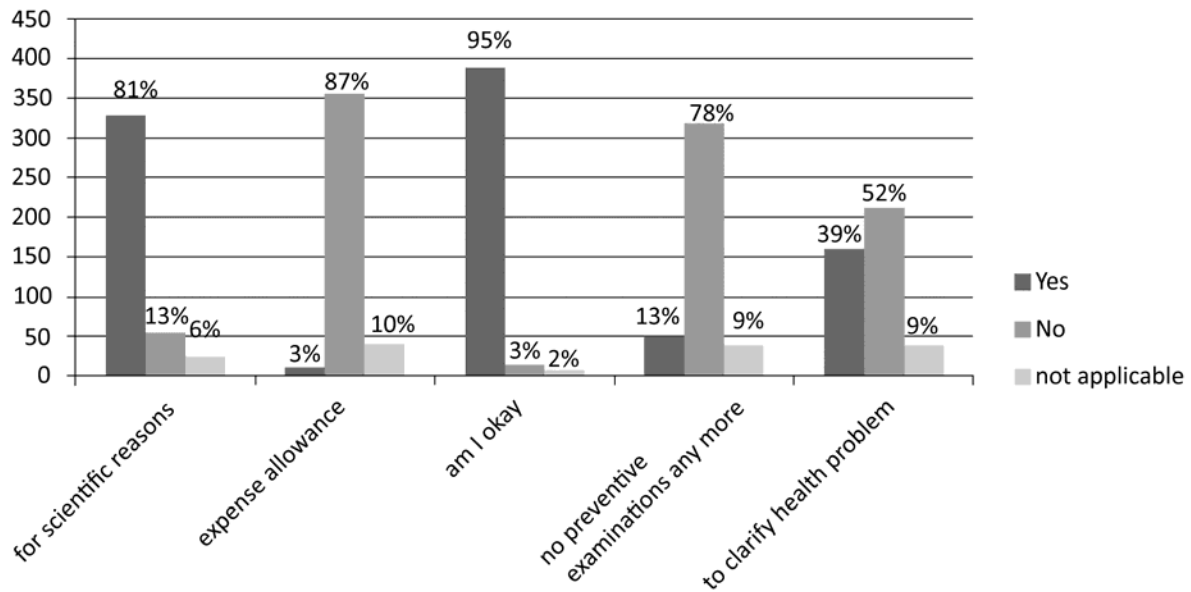
²⁰ SHIP Teilnehmerinformation, p. 14.

²¹ Ibid.

²² Kühn. *Ganzkörper-MRT*, p. 3.

When examining the answers on the questionnaires concerning the motivations that led to participation, it becomes obvious that not all of the relevant information was understood by research subjects:

Fig. 5: Motivation for participating in the MRI examination



The primary reason given by participants for their decision to take part was the hope to find out whether they are healthy (95%). The second most common motivation reported was a scientific reason (81%), and the third most common was the chance to clarify certain medical conditions (“because I have certain medical conditions and I hope that by the MRI examination the reason for that is found”) (39%). At last, 13% thought that by participating in the MRI examination they do not have to attend any medical check-ups anymore. In contrast, expense allowances seem to play only a minor part.²³

The phenomenon of the Therapeutic Misconception (TM) is detectable in this sample, despite the high quality of the IC process adopted within SHIP. This is a common phenomenon in medical research studies.²⁴ TM is the general tendency of research subjects in medical research studies to have exaggerated or false expectations concerning the personal therapeutic benefit of research participation. These expectations occur even if they are explicitly denied during IC.²⁵ The participants’ assumption that the SHIP whole-body MRI will clarify medical conditions illustrates the phenomenon of TM very well: For the research subjects the research interest takes a back seat. Although they take part for scientific reasons they want to get something “in return.” According to them, this return is finding out whether they are healthy and possibly also finding out the causes for certain medical conditions.²⁶

²³ An allowance of 20 € and travel expenses are offered to the test person within SHIP.

²⁴ cf. Appelbaum et al. *Therapeutic Misconceptions*, p.1.

²⁵ This explanation generalizes the definitions suggested for the particular context of clinical studies by Appelbaum et al. *Therapeutic Misconceptions* and Wolf et al. *Managing Incidental Findings*, with regard to managing incidental findings.

²⁶ The observation that the research subjects participated in the MRI because of something they would get in

With regard to issues of research ethics, this observation of TM is alarming. We will return to this issue later. But first, another issue raised by responses on questionnaires must be raised: Almost all participants think that they will get to know if they are healthy. This is a relatively general expectation which is not necessarily problematic. However, if this expectation is related to the number of people who think that they no longer need medical check-ups because they participated in the whole-body MRI, it becomes very problematic.

Indeed, only a few research subjects said “yes” when asked if participation in the SHIP whole-body MRI would substitute for a medical check-up (in the postal questionnaire, 52 respondents), in comparison to the 95% who noted approval of the statement “because I will get to know if I am healthy”. 23 research subjects out of these 52 received a report of incidental findings, in response to which one would expect them to pursue medical treatment. However, not all research subjects who received a report did consult a doctor in order to clarify the findings that they were told could indicate a serious disease and would need confirmation in order to identify a need for further therapy and medical supervision. 29 research subjects out of this group did not get any finding and will, if they act according to their answer in the second questionnaire, no longer attend medical check-ups, or at least decrease their attendance.²⁷

In summary, we can conclude that the stress caused by waiting for the result and the stress of receiving a result are not as high as expected. Moreover, research subjects’ evaluation concerning their participation in the MRI examination was mainly positive, and their willingness to participate again was very high. When placing these positive results in the context of other results, we can note that the very positive responses of research subjects can be attributed to the fact that they (at least in part) expected a benefit from their participation. That participants were pleased with their participation, and must therefore have felt that their expectations of therapeutic benefit were met, indicates that a significant misconception was taking place. This misconception took place despite the informed consent process, which explicitly discounted the therapeutic benefit of the study. And, apparently, research subjects encountered no occasion after that consenting process to critically question their expectation of benefit from the examination.

Qualitative Portion

Before the most important results of the qualitative portion of the study are presented, some methodological comments must be made.²⁸ After the publication of initial results²⁹ a discussion arose regarding the validity of results of qualitative (social) research in general and the representative nature of individual statements by research subjects in particular.³⁰

return is confirmed in the interviews, discussed below.

²⁷ With this in mind, it is alarming that one research subject stated in an interview that she received a notification from “Schwerin” - possibly the central department for mammography screening in Mecklenburg-Vorpommern. When she called and talked about her participation in SHIP, “Schwerin” said that the MRI examination within SHIP is even better than a mammography and that she did not have to come to a screening for the next two years.

²⁸ A detailed reflection on methods cannot be made here. However, they are an essential part of the results of the study and will be presented in greater detail in the upcoming doctoral thesis (cf. Foot note 17).

²⁹ Langanke/Erdmann. *MRT als Studienuntersuchung*

³⁰ Every participant was informed orally about the purpose of the interview and the planned scientific use. The corresponding consent documents given to the research subjects contained permission to publish the

Qualitative social research is an established method, and in this respect its legitimation is unnecessary. At the same time, this method also has its limits. The same could be said with respect to the quantitative methods of social research. The decisive issue, however, is that the usefulness of a method can only be rated in connection with its aims. The question remains what can be achieved with a particular method and which kind of conclusions can be generated and supported using this particular method:

Understanding does not start with observing or collecting data or facts, but with *problems*. There is no knowledge without problems – and no problem without knowledge.³¹

The motivation for using qualitative methods in this research study was to learn more about the effects of incidental findings on these research subjects. This aim focused in particular on questions about stress, and thus was intended to assist in the interpretation of the results of the questionnaire. The following issues needed to be clarified: How high was the stress caused by the report of incidental findings? What was the antecedent for the stress – the result itself or factors relating to the reporting procedure? However, it was never the aim to get general statements from the SHIP research subjects.

Furthermore, it has to be emphasized that questions related to a deeper understanding of the perspective of the participants, and their concrete experiences, can be answered better through a qualitative rather than quantitative approach. These methods do not generate findings that can support the development of general statements; they do not allow one to extrapolate individual answers to *all* research subjects.

Lastly, one should remember that with regard to issues of ethics, an individual case can be problematic on its own, in the sense that a relevant opportunity for improvement can be identified. As a matter of course, the measures of academic rigor have to be preserved also within empirical ethics, for the reason alone that the results will be distinct from everyday knowledge. Thus, a recourse to “casuistry” within the field of ethics is not unscientific as long it is methodically clear that individual cases cannot be presented with the claim of a representative nature.

The interviews confirm the results of the questionnaires in many sections, especially with respect to the satisfaction of research subjects with their participation in the MRI examination and their willingness to participate again.

B 13: Well, all in all, I think this is a good thing and I would be glad to participate again, if I can participate again in five years.

Some apparently contradictory responses on the questionnaires were clarified through the interviews. This was the case, for example, in interviews with research subjects who said in the questionnaire that they did not understand the written report of the findings and found this stressful. Yet, they reported that, like the majority of other research subjects, they preferred to be notified in a written report.³² A possible explanation for this discrepancy provided by the interviews was that the participants were concerned that if an oral report was

³¹ results as long as no inference from the de-identified text passages to the interviewee’s identity is possible. Popper. *Die Logik der Sozialwissenschaften*, p. 104.

³² Preferred form of report “in writing” = 199 respondents, “by telephone” = 1 respondents, “in a personal consultation” = 158 respondents.

given they would not also receive a written report they could take with them to their medical doctor.

B5: Hm. You have something to show, you know. (I: hm) If somebody had called me: “Well, you are suspected to have this and that” (I: hm), then I said: “Okay, well then?”, you know and now I can go to my doctor (I: hm) and say: “Here,” (I: hm, hm) “look”. (laughing)

The interviews also demonstrated that the procedure used within SHIP may lead to uncertainty, since written notification is only given in cases of a severe finding which needs to be followed-up, but not in cases of findings with an unclear pathological value. Not all research subjects realized that not receiving a notice reflects good news.

B4: Well, I waited and waited that I, as promised, will get a written result, like I got for all the other examinations (I: hm), but so far I haven't got anything (I: hm), that's not, well, er, what I've expected.

The following example illustrates a special case where a participant was told in the final consultation that possible indications of an aneurysm were detected. However, this respondent did not receive a written report of findings.

B24: Well, let's say in the relatively short final consultation, I had only 20 minutes with the doctor. In that time I expected a written or detailed, er, result, you know. And I took part more than one year ago. It was DDMMYY when I was there (I: hm). That's why. And because he said certain things because of the aneurysm or something, then you start worrying. Well, okay, for a short time and then you suppress it and you go back to the daily routine (I: hm) ..., you know.

Moreover, on the basis of the data from the interview it is possible to identify other stressful factors that were not anticipated stress factors, and also to identify more precisely what caused the stress has and how it affected the individual.

For some research subjects it was the time between the examination itself and the receiving of the report of incidental findings which was unpleasant:³³

B21: which was almost three hours, I think I had lain there 2.5 hours, that was okay. I don't mind being in that tube. That was perfectly okay, I like it, I would do it again any time. (I: mhm) The evaluation was okay, too. (I: mhm) When I suddenly received a letter recently, it was in February and in September now, from the MRI. That I really should do a mammography, because they detected something. I thought their diagnosis was mistaken. At first, I looked into my calendar. When had I been to the MRI (I: mhm)? I cannot believe it (I: mhm). I really did count 29 weeks. Well, I had written down every appointment. (I: mhm)

I: X [date] is in my documents.

B21: Yes, and then I counted. I did have a treatment on the 28th. I think, on September 25th I got the letter. (I: laughing) And then I thought, it's over now. (I: mhm) And if they wrote seven millimeters, in seven months the cancer doesn't grow only one millimeter, that can be far more.

I: What did the report read exactly? It was written that you have an expanding lesion?

B21: “detected in the right breast, 9 o'clock, a seven-millimeter hardening which needs clarification by a mammography.” (I: mhm) Well, I pulled out all stops, of course in order to do a mammography. I had an

33 One reason for the long time of waiting until the final analysis of the MRI images and until the incidental findings are mailed is the high quality standard within SHIP. This standard includes an independent radiological follow-up and multiple diagnosis. Moreover, the Advisory Board may be contacted.

appointment at the university hospital right the next day. Well, and then they came to the result that, fortunately, there wasn't anything

This respondent was, despite her long wait during which she did not think of the findings, lucky in two ways. Firstly, she received the report at a time when she could act immediately and make an appointment for clarification. Secondly, she actually got an appointment right away so that one day later she had the “all clear.”

In contrast, there were cases where the people concerned were highly stressed because the time of notification was very unfavourable. This is shown by the following example when the day, a Friday, had already begun with an accident for the participant:

B20: ... we wanted to visit our daughter in X that Friday, who was only living there for two months. (laughing). And we had imagined our weekend in a different way. [...] I know, the child will come home any moment and alone (laughing) her facial expression. (I: Mhm) What followed was the disappointment that we definitely can't go (I: yes). And then she got the mail from the mailbox and only the fact that she put the envelope down, I did not want to open the letter. (I: Mhm) Because I thought, if I have, well, I didn't expect at all to receive anything. I had zero expectations. (I: Yes) As I said, because I assumed that all in all everything was okay and I thought, if I receive anything, something is wrong. I wouldn't have thought that it would be a finding concerning the breast again (I: Yes). I opened it. Well, we wanted to eat then but whatever (I: laughing). (laughing) I wasn't hungry anymore. Not at all. And while reading I knew somebody is turning at the clock. You know, my mind ceased, for a bit. You refuse to believe it, and at the same time you have a tremendous fear because you don't want to go through that again. It has been so nerve-straining and then you think, ‘crap,’ again at the end of the year. There were so many thoughts and questions running through my mind which I can't reproduce. (I: Mhm) I worried most about the fact that my daughter was there because I tried to keep her out of that. (I: Yes). Because, she was 14 and then you try to withhold the information as long as possible. (I: Yes). () (laughing) (...) And at that [B20 crying] moment she knew how serious it has been in January.

In some cases research subjects were stressed by the period of time they had to wait until the suspicious finding could be clarified. It was not unusual for the clarification to take several weeks. For the respondent above, the clarification took place like this:

B20: The time frame was somewhere, you went there, after my gynaecologist persuaded me to do a tissue sample (I: Mhm). Oh, we do another MRI and then, and then the MRI should be sometime after six weeks somewhere. I said “This can't be true” and you are emotionally at the end (I: Mhm) and you actually hope that it will be quick. (I: yes) And when they say we do another MRI in six weeks. (I: Mhm) Then you think, that you won't get through this. (I: Mhm) Because, and I really was emotionally at the end, I didn't have any strength left to hide it from my family except my husband and to come up with a new story why we have to go to Greifswald again. That is so exhausting because, my sister had malignant breast cancer twice (I: Mhm) and then you try to keep your feet still (I: yes) and to not disturb anyone as long as you don't need to. (I: yes yes) But, nobody involved in science understands that. Here we go again (...) I had the feeling, it is only research, and I really had the feeling “well, we are only here because of statistical reasons and well”

Another circumstance leading to stress for the research subjects is the content of the written report. The structure of the notification does not allow for an explanation that, for example, the results are preliminary and possibly represent a false positive. Furthermore, it does not take account of the “*art*” of report information, as established in fields like oncology. There are psychologically-based approaches which can be used to deliver serious messages (“bad news”) appropriately. When a finding does indicate a cancer or other life-threatening disease, according to these approaches a face-to-face conversation among the

patient, family members, and doctor has to take place.³⁴ The fact that the written report of findings leaves people concerned, but with no way to answer their questions about their future and their health, was demonstrated clearly in this case.

However, the story of respondent B20 regarding her participation in the whole-body MRI examination contains two more aspects which are relevant for this study:

First, it was clear that the participant thought that information she provided to the research personnel in the MRI examination centre would be taken into account in the course of diagnostics:³⁵

B20: Well, let's say, beforehand you are asked some questions before going to the MRI. He asked for any problems, for any surgeries or whatsoever. I think such information is used afterwards for the evaluation of the results or it should be considered to clear up any misunderstandings. If somebody, okay wait, I have to explain this.

I: I think I know what you mean.

B20: Let's say, if I hadn't said anything about my surgery then he wouldn't have made any statements because of the findings, well no, that's not true either. He would have come to the conclusion that there is something, just like that. (I: Mhm) But because he knew, from the former survey (I: yes), one would have this drastic statement. One should have written that the MRI of the breast provided some uncertain results, please let this be clarified. (I: Mhm) But to come straight forward with this, I was scared. I don't blame you that the device didn't or that he maybe saw something different. (I: Mhm) Because, the images are maybe different (I: yes) from the ones from the mammography (I: yes, yes). But because he knew that a surgery was done, diseased tissue was removed there and a new one developed, despite all that the classification was almost malignant. Maybe, the report should have been written in a different way. There is, do you understand? (I: Mhm). There are some discrepancies, please let the finding be clarified or whatsoever. Definitely, I would have appreciated not being placed in that position.

The respondent's assumption that the research interviewer was taking a medical history for care has to be interpreted as evidence of TM. There were a number of other hints of TM in the interviews. A detailed discussion of these statements, and the uncertainties associated with their interpretation, cannot be fully addressed here.

We can also see that the interview with respondent B20 raises a number of issues related to false positive findings. This issue is important because, on the one hand, it is problematic that the research subject did not understand information she was given that the whole-body MRI examination can result in false positive (and also false negative) findings.

On the other hand, though, it is not possible to directly clarify unclear findings in the MRI examination centre. Immediate follow-up is forbidden by the ethics committee because the hospital is not allowed to generate patient visits through SHIP. This circumstance leads to a period of stressful waiting for some research subjects.

This is also concerning because controversy remains around the sensitivity of the MRI for certain organ systems. If, for instance, an anomaly of the breast is detected in a SHIP participant using the whole-body MRI, this person receives a report about the incidental findings, and afterwards should consult a local doctor. This doctor will then order a mammogram. If this mammogram does not show any anomalies which need further clarification, it is, as a matter of course, assumed that the MRI generated a false positive

³⁴ Cf. in particular Fallowfield/Jenkins. *Communicating*, or Baile et al. *SPIKES*.

³⁵ Taking an informed consent consultation for a medical interview has to be classified as a hint of TM, too.

result. However, this conclusion is only sound if the devices used in gynaecological/radiological practices, where a mammogram is done, are sensitive enough to really confirm or disprove the finding from the MRI. This is a controversial issue within the field of radiology. This conclusion that a false positive result has been generated could easily be reversed if it is proven that the MRI is more sensitive than mammography in detecting neoplasms of the breast.

Summary of Results

Only three percent of the research subjects stated that the waiting stressed them “quite a lot” or “very much”. 25% of those who received a report about incidental findings stated that they felt “moderate” or “heavy” emotional stress caused by this notification. The analysis of interviews with those who reported very high stress in the questionnaires showed that the reasons behind the stress can often be identified. From this, we can conclude that the stress is not caused only by the result itself or the consequences following it. Instead, the following stresses that were observed could be preventable or reducible:

- a) stress resulting from the policy no written notifications are sent if no anomalies are detected
- b) stress caused by waiting until the report is received
- c) stress caused by the content of the report
- d) the long wait following the report until the finding can be clarified.

Moreover, it has to be emphasized on the basis of the study results that satisfaction with participation in the whole-body MRI is overall very high and that those research subjects who were very stressed were still willing to participate again.

When asked to identify risks and disadvantages, many participants cannot think of anything - even if, for instance, if they had to endure great fear (in retrospect unnecessarily) because of a false positive result. This is also seen as evidence for TM, which would be characterized by an overvaluation of the individual benefits of participant and an underestimation of risks and disadvantages:

I: So, what outweighs is...

B20: The value.

I: The value.

B20: Yes.

I: Despite everything.

B20: Despite everything.

I: Okay.

B20: Yes, well, as I said, there is always a little fear left but, after all, I am more calm now.

Research ethics implications for GANI_MED

A significant aim of this study was to take lessons learned from these findings and apply them to the development of GANI_MED. While the findings themselves are observations, we

could use them in the development of policies by linking them with ethical principles related to human research subjects (cf. 6.2).³⁶

An example of a policy informed by these findings is the institution of regular trainings for research staff conducting informed consent sessions for GANI_MED. This trainings focus, among other topics, on sensitizing staff to the problem of TM.

Given that the GANI_MED project also involves MRI evaluations performed for research, rather than clinical care, purposes, we developed a set of policies designed to guide reporting of incidental findings:

- We developed and distributed a detailed set of standard operating procedures (SOP) for reporting incidental findings.
- The process of notification was designed in consultation with psychologists and other experts experienced with “breaking bad news.”
- Research subjects with no identified anomalies are explicitly notified of this finding. This notification also contains an explanation that pathological findings can be “overlooked” in these studies, and a recommendation for participants to continue routine check-ups and to consult a doctor if they develop any new symptoms.³⁷
- Notifications are not provided in written form alone unless circumstances prevent notification through other means, such as when the participant cannot be reached by phone within a reasonable time, or when the participant has explicitly requested this.
- Participants are called to schedule an appointment to have a face-to-face consultation in which their findings will be returned. Information about the finding is not provided by phone.
- A set of guidelines define the period of time that may pass between an MRI exam and the report of findings to participants. If study procedures, such as reviewing images and scheduling appointments, fall behind MRI exams such that reports are not being returned within the designated period, MRI exams are placed on hold until other procedures can “catch up.” Alternatively, research subjects must be informed of delays.

Ethics issues relevant to incidental findings

As a summary and conclusion to this report of empirical findings, we will provide a brief discussion of the issues of professional ethics related to incidental findings in research. In addition, we will review the regulatory basis (cf. section 5) for the recommendations the chair of Systematic Theology, Greifswald provided to the GANI_MED team related to incidental findings.

³⁶ Because one can only derive norms from premises which already contain norms there is no logical alternative to adding the commandments, prohibitions and permissions (i.e. norms) to ethics regarding research subjects. For the problem of “is” and “ought” cf. Wimmer. *Naturalismus*, pp. 965-966 for an introduction.

³⁷ For the wording of the relevant cover letter cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, pp. 236-237.

Incidental findings from MRI as a research ethics problem

In the German-speaking space, M. Hoffmann and R. Schmücker have dealt with the ethical aspects of incidental findings generated through MRI exams in observational studies in their article *Die ethische Problematik der Zufallsbefunde in populationsbasierten MRT-Studien* (*The ethical problem of incidental findings within population-based MRI studies*).

According to Hoffmann and Schmücker, the primary ethical problem relevant to incidental findings is not the possible stress they may introduce for research subjects and the possible development of a TM. Rather, they focus on the ethical conflict between the interests of the participants, who will possibly not be notified about relevant health information, and the interests of future generations of patients, who will benefit from the results of observational health studies. This conflict is, according to them, even more precarious because the report of findings compromises the validity of an observational study. This is because the report of findings alters the interventions conducted within the observed population:

If a study is conducted with the intention of informing the care of future patients, then these results can be damaging if they methodological shortcoming lead to incorrect findings. This type of research must therefore follow the best available standards with respect to methodological quality.³⁸

In light of this opinion, one of the solutions discussed is *not* to report any incidental findings, in general. Instead, “monetary motivation” for participation should be provided.³⁹ An alternative solution would be to explicitly differentiate between incidental findings which must be reported and those that do not need to be reported.

From our point of view, it is more ethically appropriate to return some results, and therefore to differentiate between incidental findings which should be reported and those that should not be reported. However, this approach would depend on additional research; it presupposes the development of an inventory of findings that have been evaluated for their suitability to be returned. Using such a resource study personnel could reasonably distinguish between incidental findings which must be reported and those that do not need to be reported.⁴⁰

The protocol for SHIP adopted this second option. Within SHIP, follow-up studies are used to further clarify diagnoses. In addition, an Advisory Board is used to develop policies and identify findings that should or should not be reported.

However, even study settings utilizing carefully designed protocols can create a high level of stress for some research subjects, as the results of our study show. More importantly, though, incorrect assumptions concerning the personal benefit of participation can lead to actions (such as not attending medical check-ups) that are harmful to the participant’s well-being. In fact, this phenomenon was more common in our sample than elevated stress. In light of this, and also in view of the occurrence of stress that is preventable or reducible, serious ethical issues are raised by incidental findings. These problems must be solved via applied ethics in the area of human research protections.

³⁸ Hoffmann/Schmücker. *Ethische Problematik*, p. 19.

³⁹ Hoffmann/Schmücker. *Ethische Problematik*, p. 15.

⁴⁰ Hoffmann/Schmücker. *Ethische Problematik*, p. 20.

Disclosure of incidental findings from MRI as an ethical problem of human research protection⁴¹

If in the design of a biomedical research study it is decided – for whatever reason – to reject a strict non-disclosure strategy⁴² and instead to notify participants of some MRI incidental findings, our findings indicate that certain measures should be taken in order to reduce stress and support a more realistic evaluation of the benefit of participating by research subjects.

We believe everyone can agree on these measures if we agree on three basic research ethics norms: a) The informed consent as agreed on prior to performance of whole-body MRI should be treated as a contract-like agreement between the institution doing the study and the research subject (“contract principle”). In addition, two basic standards of fairness apply: (b) the requirement for transparency and (c) the requirement to minimize anticipated stress.

Contract Principle

Participating in a whole-body MRI within SHIP is, of course, voluntary. Research subjects are chosen at random and are invited to participate in the whole-body MRI under certain conditions. These conditions are explained in an information document and communicated during several face-to-face conversations. If research subjects accept these conditions and decide to participate, they enter into a relationship with the study as autonomous adults. This relation is contract-like because the research subjects may rightly expect getting something in return - under the stated conditions - as promised in the official document and in the consultation with the medical staff of the study. The main reward within SHIP is arguably the notification of health-relevant information.

That one must agree to participate in SHIP and the MRI exam by entering into a contract-like relationship defines very little about what the content of that contract-like relationship will be. The contract principle places first and foremost a *formal* demand on those engaging in the contract; that both sides in the contract must keep their agreements, referred in the legal tradition by the famous formula "*pacta sunt servanda*".

Other demands with respect to the content of that agreement become methodologically important when two basic ethical norms are raised in connection with the content of the consent and the way it is presented to participants. These norms can be summed up, with few presuppositions, under the heading of “fairness”.⁴³

⁴¹ This paragraph refers to the basis given in the presentation by Langanke/Erdmann. *MRT als Studienuntersuchung*, pp. 209-221.

⁴² A great deal of ethical and pragmatic justification can be provided to reject a strict non-disclosure strategy (cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, pp. 206-207). Also Hoffmann and Schmücker. *Ethische Problematik*, p. 16 emphasize that this option is not unproblematic (selection of samples, taking advantage of the financial distress of research subjects). Moreover, if a non-disclosure strategy is chosen, research images would have to be stored separately from clinical records, so that the ethical problem will not be “passed on” to those who have to work with images in the future and may discover relevant health information.

⁴³ This beginning of reason with this architecture of principles does not have a lot of premises because it does not refer to theological arguments or higher principles from the tradition of philosophical ethics. Furthermore, the principles of bioethics basis, as defined by Beauchamp/Childress (*Biomedical Ethics*, p. 99-287), are not applied here to the problem of incidental findings within a research context. The reason for this is the fact that the “beneficence/non-maleficence” principle is not applicable for a research context. For instance, one could argue against the transferability of this principle with Heinemann et al. *Zufallsbefunde* and *Zufallsbefunde Supplement*. They say that the relation between a researcher and a research subject is not like the relation between a doctor and a patient so that researchers do not owe their research subjects

Transparency requirement

In order to obtain an ethically valid IC research subjects and patients who participate in scientific studies should be able to understand a) which conditions govern their participation and b) which consequences of their participation can be anticipated.⁴⁴ These two dimensions have to be distinguished. Transparency is required both with respect to the format and wording of the information participants are provide, and also with respect to the way the consequences of decisions are emphasized and discussed.

Whoever agrees with this norm of transparency in both of its aspects must also admit that the IC documents should be *as transparent as possible*. But by saying “*as transparent as possible*” we are implicitly admitting that “transparency” is an ideal; we cannot demand that *complete* transparency be obtained in all cases. However, since transparency is the sort of thing can than be realized to a greater or lesser degree (an IC document can be “more or less transparent”), then in our research practices we can demand that transparency should be *improved*.⁴⁵

Requirement to minimize anticipated stress

The transparency norm demands that anticipated consequences must be communicated as clearly as possible. On the other hand, the principle to minimize anticipated stress requires that anticipated stresses should at least be minimized in the course of potentially stressful study processes (e.g. the process of reporting incidental findings). But only anticipated stresses can be reduced, and the ability to minimize stress is constrained by the practical context of the study, e.g. the limited staff, time and finances in medical studies.⁴⁶

From our point of view, the plausibility of the requirement to minimize anticipated stress is supported by the fact that its validity can be disputed only at the cost of a gross contradiction against prevailing moral institutions, if three conditions are met:

- Certain processes within the study can be stressful for the research subjects and to cause this stress is not the purpose of the study.
- This stress can be, if not completely preventable,⁴⁷ mitigated if the variables that influence this stress are known.
- Modifications in research protocols intended to minimizing of stress can be implemented using the known variables with appropriate effort within the given financial and staffing resources without jeopardizing the purpose of the study.

Due to reasons of space, we will not demonstrate in detail how this suggested structure with respect to principles of research ethics, in combination with the empirical findings presented in this paper, support the policies described in section five with respect to the design of

the same as patients rightly expect from their doctor.

⁴⁴ cf. also *Deklaration von Helsinki*, § 22 or for the German context *Bundesärztekammer*, ch. 5; 8.

⁴⁵ For “transparency” as an ideal and the role of TM as a practical limit of optimizing cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, p. 214-216.

⁴⁶ For criteria of the possibility of anticipation cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, p. 217.

⁴⁷ If it is admitted that stress from the report of findings cannot be absolutely preventable because the report of a potentially pathological finding always causes anxiety and fear.

GANI_MED.⁴⁸ At this point it should be noted that it is characteristic for the empirical/normative approach of the team at the chair of Systematic Theology, Greifswald to supplement classical normative argumentation with reflection on results from empirical research. With this combination of normative and empiric methods the chair of Systematic Theology contributes to what is currently discussed and disputed under the topic “empirical ethics”.

Summary

The understanding of persons who participated voluntarily as research subjects in the population-based SHIP in a whole-body MRI examination is not well developed, in the sense that they did not appear to recognize the risks and disadvantages which *can* be part of the examination. From this we may assume that they did not understand at least some of the information they were provided in the informed consent process. This is the conclusion of this empirical study undertaken to explore the aspects relevant to ethical issues in the reporting of incidental findings generated in the course of MRI examinations conducted as a part of epidemiological research.

The analysis of questionnaires and interviews demonstrated an extremely high level of satisfaction and a corresponding willingness to participate again in an MRI study. Despite the fact that “customer satisfaction” was very high, this study also indicates that the positive perceptions of the study are a result of a tendency of research subjects to overestimate the study’s diagnostic benefit, despite being provided information to the opposite. The benefits they expected are not validated for many types of findings made through whole-body MRI. Almost 40% of the questioned participants assume that medical conditions will be clarified through this examination, and 10% think that they do not require further medical check-ups because of their participation in the whole-body MRI. These results, which show an overestimation of the benefit (and an underestimation of possible risks) by research subjects in the sample we examined can be attributed to the phenomenon of *therapeutic misconception*, a phenomenon well recognized in a variety of types of biomedical research studies.

In summary, we conclude that a) the assumption that the reporting of the incidental findings will cause a disproportionate stress for the research subjects *cannot* be confirmed on the basis of this sample. However, from a research ethics perspective, we can say that b) potential stress can be prevented by various measures, such as through changes in the methods used for reporting results. In addition, c) the process of informing research subjects of the risks and benefits of research must be improved so that research subjects are able to evaluate the validity of results from whole-body MRI more realistically.

Acknowledgements

For a critical revision of the manuscript and important suggestions regarding content and method we like thank Prof. Dr. Henry Völzke and Dr. Carsten-Oliver Schmidt (SHIP). We

⁴⁸ Cf. Langanke/Erdmann. *MRT als Studienuntersuchung*, p. 218-221.

would also like to thank Wenke Liedtke *can. theol.* for providing the illustrations and Antje Holtmann for the translation into English.

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