Should the governance of individual treatment attempts (“Individuelle Heilversuche”) include praxis evaluation? Results from qualitative stakeholder interviews.

Alice Faust 1,2* (MD; female), Dr. med. Lena Woydack 1, (MD; female), Prof. Dr. med. Dr. phil. Daniel Strech 1 (MD, PhD; male)

1 Berlin Institute of Health at Charité – Universitätsmedizin Berlin, QUEST Center for Responsible Research, Anna-Louisa-Karsch-Str. 2, 10178 Berlin, Germany
2 Medizinische Hochschule Hannover, Institut für Ethik, Geschichte und Philosophie der Medizin, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

*Corresponding Author: alice.faust@charite.de, +49 030 450 543675

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Author’s contributions: AF and DS participated in the conceptualization of the interview study. AF, LW and DS developed the interview guide. AF conducted the interviews and was supervised by LW and DS. AF and LW analyzed and interpreted the data. AF wrote the first draft of the manuscript. DS and LW supported to revise the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate: All the interviewees provided written consent to participate and the research ethics committee (Forschungsethik-Kommission) Campus Benjamin Franklin - Charité Universitätsmedizin Berlin approved of our study (EA4/005/21).

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Introduction: Individual treatment attempts (ITAs) are a German concept for the treatment of individual patients by physicians with nonstandard therapeutic approaches. ITAs span from nonstandard off-label drug uses to first-in-human uses of newly developed drugs/interventions. Due to the lack of evidence, ITAs come with a high amount of uncertainty regarding the risk-benefit ratio. At present, no prospective review and no systematic retrospective evaluation of ITAs are required in Germany; therefore, no opportunity exists for the basic evaluation of the frequency, type, or outcomes of ITAs. Our objective was to explore stakeholders’ attitudes toward the retrospective evaluation (monitoring) or prospective evaluation (review) of ITAs.

Methods: We conducted a qualitative interview study among relevant stakeholder groups. We used the SWOT framework to represent the stakeholders’ attitudes. We applied content analysis to the recorded and transcribed interviews in MAXQDA.

Results: Twenty interviewees participated in the study. The interviewees pointed to several arguments in favor of the retrospective evaluation of ITAs, such as the knowledge gain about and setting and circumstances of ITAs. At the same time, the interviewees expressed concerns regarding the validity and practical relevance of the evaluation results. The viewpoints on review addressed several contextual factors (e.g., different medical disciplines) that should be acknowledged when judging the necessity of a review.

Conclusion: One main conclusion is that the current situation with a complete lack of evaluation insufficiently reflects safety concerns. German health policy decision makers should be more explicit about where and why some sort of evaluation is needed or not needed. Another conclusion is that there is no one-size-fits-all model for evaluating ITAs. Both prospective and retrospective evaluations should be piloted in areas of ITAs with particularly high risks and conflicts of interest, such as in the application of very experimental therapies (e.g., bench-to-bedside applications) outside clinical trials.

Keywords: Individual treatment attempts, innovative care, nonstandard therapy, medical ethics, German health care system, evaluation, review, monitoring

What is already known on this topic? In Germany, the concept of individual treatment attempts (ITAs) or “Individuelle Heilversuche” exists for the treatment of patients when standard therapies have failed. At present, no systematic evaluation of the practice, setting and circumstances of ITAs exists.

What this study adds? This is the first study to qualitatively investigate stakeholder viewpoints for and against the retrospective or prospective evaluation of ITAs.

How might this study affect research, practice or policy? This study is intended to raise awareness of the lack of data and guidelines that are needed for the responsible governance of medical care affected by high uncertainty, risks, and conflicts of interest. The study results further provide a reference to guide future discussion and policy development on whether, how and where ITAs should be accompanied by evaluation.
Introduction

In 2015, a seven-year-old child suffering from junctional epidermolysis bullosa (JEB) was admitted to the Children’s Hospital in Bochum (Germany) [1]. The child’s condition worsened because of severe bacterial infections, and he eventually experienced an epidermal loss of 80%. All therapeutic options had failed [1]. In such desperate situations, physicians in Germany can conduct individual treatment attempts (ITAs, in German: “Individuelle Heilversuche”). In the case of the boy, the physicians transplanted his skin regenerated with transgenic epidermal stem cells. This procedure was highly experimental and had only been used twice in other humans before. No clinical trial had previously investigated this intervention, and no trial was ongoing at the time.

ITAs are a German concept for the treatment of individual patients by physicians with nonstandard therapeutic approaches [2]. The German Federal Supreme Court defines the medical standard as follows: “The respective state of scientific knowledge and medical experience that is necessary to achieve the medical treatment goal and has proven itself in testing” [3]. Scholars ethically justify ITAs as an ultima ratio method that is deployed when all therapeutic options have failed or there is no standard therapy available [4, 5]. The term nonstandard therapy is very broad, and thus, ITAs span from nonstandard off-label drug uses to first-in-human uses of newly developed interventions.

As nonstandard therapies often lack evidence from clinical trials, ITAs are associated with increased uncertainty regarding their risk-benefit ratio [2]. This uncertainty addresses several ethical challenges [6] that have also been discussed in the context of experimental or unapproved therapies [7-9], off-label uses [10, 11], or first-in human therapies [12]. For example, the higher the uncertainty is, the more intuition-based the assessment of risks and benefits. Intuitions are susceptible to different kinds of bias and can thus increase the likelihood of misjudgment about risks and benefits [13].

In other contexts of medical care that are prone to high levels of uncertainty (e.g. organ transplantations, care of premature infants) or in medical research, the actual effects of practices are often evaluated retrospectively based on systematic documentation [14, 15]. International guidelines such as the Declaration of Helsinki (paragraph 37) recommend documentation and evaluation as basic ethical principles for treatment attempts with individual patients with high uncertainty [16]. For ITAs in Germany, no form of systematic documentation and thus no retrospective evaluation for ITAs exist. At present, it is impossible to know what and how many ITAs have been conducted in Germany. As a consequence, no evaluation exists about how often ITAs (in a certain therapeutic area) result in substantial health benefits and/or severe side effects.

Furthermore, guidelines, e.g., from university medical centers and professional societies in the USA, suggest a form of prospective review of innovative care attempts to ensure patients’ safety [17, 18]. While several ITAs in the German context might be classified as innovative care, no standardized process for an independent review exists in Germany. The possibility of contacting a clinical ethics expert for physicians who want to conduct ITAs is mentioned on the web pages of a few university medical centers [19, 20].
We conducted a qualitative interview study to explore stakeholders’ attitudes toward retrospective evaluation (monitoring) and prospective evaluation (review) of ITAs. We categorized these attitudes in terms of strengths, weaknesses, opportunities and threats (SWOTs). Furthermore, we gathered stakeholders’ suggestions for different options regarding retrospective or prospective evaluation.

Methods

Ethics approval: The research ethics committee of Charité Universitätsmedizin Berlin approved our study (EA4/005/21).

Sampling: We used a purposive sampling strategy combined with a snowballing approach to identify potential participants with different backgrounds relevant to the topic of ITAs (physicians, bioethicists, a legal expert, a health care insurance representative, patient representatives, and representatives of the level of self-administration in the German health care system). The initial sampling strategy included searches across webpages of different hospitals and stakeholder groups as well as the professional networks of DS and LW. Invitations (supplementary 1) together with a consent form (supplementary 2), study information (supplementary 2) and a data protection declaration (supplementary 2) were sent out via e-mail.

Procedure: We performed qualitative in-depth interviews [21] that lasted between 30-50 minutes between March and November 2021. We used audio-recorded video or phone calls for the interviews and took field notes during the interviews. The audio recordings were transcribed by the company Amberscript under a data processing agreement. The participants did not provide feedback on the findings. A physician (AF) with experience in qualitative research conducted all interviews. Both LW and DS, both physicians and experienced qualitative researchers, were present during 5 (LW) and 5 (DS) interviews to supervise and support AF. We developed a first interview guide with open questions for the semistructured interviews [22]. We slightly adapted the initial interview guide after conducting 10 interviews with mainly clinicians and some ethicists. In the first version of the guide (see supplementary 3), we asked about different aspects of a retrospective evaluation (e.g., documentation or data use) separately. We adapted the interview guide (see supplementary 4) because the interviewees did not address the different aspects of retrospective evaluation (e.g., documentation) separately, and a slightly adapted procedure was necessary for interviews with stakeholders from nonclinical areas.

Data analysis & definitions: AF analyzed the transcripts with MAXQDA using content analysis [23]. LW read all the transcripts and double-coded difficult passages. AF and LW discussed the coding results. Only minor discrepancies occurred, and they could all be resolved through discussion. We discussed the codebook and the results in the whole team (AF, LW, DS) multiple times until everyone agreed on the final codebook. We employed deductive and inductive category formation [24]. The deductive categories “retrospective evaluation/monitoring” and “prospective evaluation/review” were extracted from the interview guide. As first-order subcategories, we used “SWOTs” and “Strategies” for retrospective and prospective evaluation. Second-order and further subcategories were derived in an inductive manner directly from the material. From interviews with physicians, we obtained additional
results on subtypes of ITAs. We summarized these results under the theme "Categories of ITAs." Thematic saturation was reached at interview 17, when no new themes could be identified [25].

Table 1: Our definition of SWOTs is based on a definition employed by Wieschowski et al. [26]

|                 |                                                                                           |
|-----------------|--------------------------------------------------------------------------------------------|
| **Strengths**   | The inherent qualities of prospective and retrospective evaluation that have a positive impact on patients, the health care system, or the public in general. |
| **Weaknesses**  | The inherent qualities of prospective and retrospective evaluation that are harmful for patients or the health care system, or the public in general. |
| **Opportunities** | The external and procedural factors that could support an implementation of a prospective and retrospective evaluation of ITAs. |
| **Threats**     | The external and procedural factors that could threaten an implementation of a prospective and retrospective evaluation of ITAs. |

What we classify as SWOTs in each case reflects the opinions of the interviewees and not necessarily the authors' opinions.

**Results**

We invited 56 people to participate, of whom 20 from different professional areas participated. The physicians had varying degrees of professional experience, and all worked at university medical centers. See table 2 for the participants’ characteristics.

Table 2: Participant characteristics

|               | 20*     |
|---------------|---------|
| **Total**     |         |
| **Gender**    |         |
| Male          | 14      |
| Female        | 6       |
| **Stakeholder group** |       |
| Physician     | 12      |
| Bioethicist   | 3       |
| Legal expert  | 1       |
| Health care insurance representative | 1 |
| Representative of the level of self-administration in the German health care system | 3 |
| Patient representative | 2 |
| Clinical area (of) |         |
We structured our results under the following three themes: “Retrospective Evaluation (Monitoring)”, “Prospective evaluation (Review)” and “Categories of ITAs”. In the following, we present the key points of our findings that were discussed most intensively or extensively by the interviewees in a narrative form. For the spectrum of all our identified themes, see Tables 3 (E1-45, R1-15) and 4 (S1-S3), which give example quotes for every identified code.

**Retrospective Evaluation (Monitoring)**

**Strengths**

*System responsibility*

Interviewees described several reasons why a basic form of retrospective evaluation of ITAs is an important element of system responsibility. Interviewees, for example, mentioned that a certain form of basic retrospective evaluation of the practice and settings of ITAs would provide important insights that the German health care system currently does not provide (E1). The results of such a basic retrospective evaluation could be used to develop best-practice standards for ITAs that currently do not exist (E2). The systematic documentation of ITAs could further facilitate the sharing of ITA-related experiences with medical peers (E5). An ethicist suggested that the development of standards for retrospective evaluation of ITAs would also become relevant for the evaluation of personalized therapies (E7).

*Knowledge gain about the intervention used*

According to the interviewees, a basic form of retrospective evaluation of ITAs would provide relevant information about the interventions used in an ITA (E8). Some interviewees pointed to the particular interest in gathering data and documenting experiences for ITA interventions used to treat orphan diseases (E8). Some interviewees saw the possibility of a retrospective evaluation as a chance to also make information about negative outcomes of ITAs available for other physicians and scientists. These interviewees complained that, otherwise, only successful ITAs with positive results are published, e.g., as case reports (E10). Furthermore, interviewees suggested that data collected during the conduct of ITAs could serve as a basis to generate hypotheses for future research (E11). Some interviewees mentioned that in rare cases, the results of ITAs could even be used for certain authorization purposes (E12).
**Weaknesses**

**Validity and practical relevance of evaluation results**
Several interviewees were skeptical about the validity and usefulness of retrospective evaluation results (E13-E17). One interviewee mentioned that the data they would gather and then evaluate would be derived from nonideal circumstances in clinical practice and therefore be probably biased in different ways (E15). Another interviewee emphasized the retrospective nature of the data collected in ITAs as a weakness for their usefulness (E14). Interviewees were worried that, in general, it would be difficult to determine which effect to attribute to the drug used in an ITA because, for example, patients treated through ITAs are often treated with several drugs at the same time (E16c). They also pointed out that it might be hard to differentiate between side effects due to the drug or intervention used or a worsening of the patients’ condition due to the natural progression of the often-severe disease (E15b).

While referring to one or more of the above-described challenges, some interviewees questioned whether an intervention-specific retrospective evaluation of ITAs would enable them to draw more general conclusions regarding the risk-benefit ratio of a specific intervention used in an ITA (E16c). Some interviewees went even further and highlighted that because ITAs are so individual, it would be difficult to gather any generalizable information on the effects of ITAs (E16a-b).

**Difficult distinction between ITAs and research**
Some interviewees were critical of the idea of a retrospective evaluation of ITAs because it might be perceived as contradicting the concept of ITAs as a form of therapy and be seen as research instead (E19).

**Strategies for retrospective evaluation**

**Goals of evaluation**
Some clinicians and other stakeholders were interested in an “intervention-specific” retrospective evaluation of ITAs (E22) because this would allow the sharing of experiences with other physicians who had already conducted or planned to conduct similar ITAs (E22b). One interviewee highlighted that evaluating ITAs has become increasingly important for genomic therapies that are specific for individual patients (E22a). Another contrasting idea mentioned by the interviewees was an “intervention-overarching” retrospective evaluation of ITAs. The interviewees in favor of this strategy stressed the importance of determining general facts about ITAs, e.g., in which types of patients ITAs are conducted or how many ITAs are conducted each year. (E21). Such an “intervention-overarching” retrospective evaluation would not assess the effects of a specific intervention used in an ITA but the effects of ITAs as a more general type of intervention/measure in clinical practice.

**Evaluation method**
The interviewees suggested not focusing only on quantitative retrospective evaluations of ITAs but also performing qualitative evaluations to obtain deeper insight into the motivations and circumstances of ITAs (E23). Some interviewees mentioned the possibility of a registry for ITAs (E24), and they had different ideas about the content of the registry, who should complete it and who should have access to it.
Opportunities

Stakeholders involved in evaluation
The interviewees highlighted that several factors, such as sufficient time (E38), financial allowance (E39), mainly automated documentation (E40), support from specific staff if possible (E42), and certain obligations for documentation, might all contribute positively to a successful retrospective evaluation of ITAs. A participatory approach that involves physicians in the design of retrospective ITA evaluation strategies was further described as a potential facilitator (E36).

Structural factors
The interviewees saw it as an opportunity that many patients whom physicians try to treat with ITAs are willing to share their data and are often not scared by potential data security issues (E43).

The legal expert saw no contradiction in retrospectively evaluating ITAs and the concept of an ITA. He argued that retrospectively evaluating the results of an ITA would not change its intention to primarily treat a patient instead of doing research and therefore would not bear the risk of being mistaken for research (E45).

Threats

Resource scarcity
The interviewees mentioned different hindering factors, such as a lack of time for a retrospective evaluation due to an already high workload of physicians (E28), a lack of money to finance a registry (E27) and other bureaucratic obstacles (E26).

Conflicts of interest
Conflicts of interest were described as another potential barrier for the successful implementation of retrospective evaluation. According to the interviewees, conflicts of interest could arise between, e.g., scientists, the pharmaceutical industry and insurance companies (E29). Moreover, the interviewees were worried that physicians could be reluctant to share the results of an ITA or the results of a retrospective evaluation of that ITA because they would want to publish the results on their own to use them for their academic careers (E30).

Prospective Evaluation (Review)

Strengths

Good practice for safeguarding favorable risk-benefit ratios
The interviewees pointed out that another expert opinion on whether a certain treatment option with high uncertainty provides a favorable risk-benefit ratio could be seen as a standard element of good practice in ITA decision making (R2).

Support of rational risk-benefit assessment
Some interviewees mentioned that a review of risk-benefit judgments can be of particular importance to safeguard rational decision making in situations where physicians who consider ITAs for their severely ill and desperate patients with no other treatment options often feel a strong emotional motivation to offer any possible help (R1).

**Weaknesses**

Some interviewees mentioned that a review, especially an obligatory one, could be seen by physicians as too strong a control of their work and an intervention in their sphere of competence (R9). Another important weakness perceived by some interviewees was a negative influence on the individual physician–patient relationship (R4).

**Strategies for review implementation**

Some interviewees pointed out that the need for and the most suitable format of reviews depend on the context of the ITA (R6-7). This context, however, is often not known because Germany lacks any systematic documentation of ITAs. Other interviewees stressed that the option of obtaining a review by an interdisciplinary board is valuable (R11).

**Categories of ITAs**

The comments from the interviewees on the circumstances under which they conduct ITAs and on their overall understanding of ITAs allowed the identification of three categories of ITAs:

- nonstandard off-label use (S1), e.g., drug repurposing in translational oncology (S1c) or for novel diseases in intensive care medicine (S1a);
- interventions that have been tested in at least phase II or phase III trials but that have no authorization in Germany, the European Union or at all (S2);
- highly experimental treatments, from bench to bedside, e.g., new substances that are directly created in the respective laboratory of an oncology center (S3).

**Discussion**

We performed 20 in-depth interviews between March and November 2021 to explore stakeholders’ attitudes toward retrospective (monitoring) and prospective (review) evaluations of ITAs in Germany. Neither type of evaluation is currently applied for ITAs in Germany, but these types of evaluations are often applied in similar health care (e.g. organ transplantations, care of premature infants) [14, 15] and research contexts that involve substantial risks, high uncertainty about the likelihood and extent of benefits, and conflicts of interest. The interviewees pointed to several arguments in favor of retrospective evaluation of ITAs, such as the knowledge gain about the setting and circumstances of an ITA and about the types of intervention used. At the same time, the interviewees expressed several concerns regarding the validity and thus the practical relevance of the documentation of ITA cases. The limited validity of documented cases could in turn bias the results of retrospective evaluations. The viewpoints on the prospective review of ITAs addressed several context
factors (e.g., medical discipline) that need to be acknowledged in judgments on where review might be more or less needed. They indicated that a review might be necessary for some subgroups of ITAs but that the subgroups are still insufficiently defined. We focus on retrospective evaluation in the discussion because the interviewees discussed this type of evaluation in more depth than prospective evaluation. There was no overall difference in the interviewees’ opinions based on their professional backgrounds.

ITAs involving highly experimental treatments that have not yet been tested in clinical trials might be defined as a subgroup. However, more research is needed to define relevant characteristics for the definition of possible subgroups of ITAs. A systematic documentation of ITAs, such as registry-based documentation, could be piloted for this subgroup. Starting with this subgroup of ITAs also has a strong ethical rationale, as such highly experimental ITAs come with particularly high uncertainty about the risk-benefit ratio [2] and often involve substantial conflicts of interest because those applying the experimental treatments can also be involved academically or even financially in the treatment’s development.

It is likely that most patients are willing to take higher risks in the face of death or severe disability. Furthermore, the determination of what counts as a benefit in such contexts cannot simply be measured in terms of decreased mortality. In the Introduction, we mentioned the example of a highly experimental ITA that was a tremendous success [1]. In another highly experimental ITA, an IgG-based bispecific antibody was given to three patients with metastasized prostate cancer. This led to a reduction in PSA levels (a serum marker for prostate cancer). Whether this surrogate outcome also resulted in patient-relevant outcomes is unknown [27]. We know about these two examples because they were described in scientific publications. Whether these ITA examples are very rare cases in Germany or whether multiple similar cases exist that were not published because of negative outcomes is unclear. Our results indicate that highly experimental ITAs are conducted, but we do not have data about the extent to which they are conducted. Only standardized documentation and retrospective evaluation would allow us to understand the complete picture of benefits and risks resulting from highly experimental ITAs in Germany. However, other scholars have already suggested the concept of a “controlled ITA”, which includes systematic documentation for risky therapies such as somatic gene therapies [28] or xenotransplantation [29].

While several interview participants had positive attitudes toward the documentation of desired and undesired outcomes of ITAs, often the same participants as well as other participants expressed concerns about the validity and practical relevance of the documentation results. The primary goal of ITAs is to treat patients and not to generate generalizable knowledge [30]. The use of innovative therapies (e.g., ITAs) that have not been scientifically validated may lead to an under- or overestimation of their risks and benefits [31]. While the reporting of the context and results of ITAs cannot substitute for clinical trials, the information could serve as a supplement or precursor to scientifically generated data. Furthermore, standardized documentation and the fact that certain ITAs will be evaluated retrospectively could function as an incentive for quality improvement and safety. “Clinical research is one kind of learning activity that might warrant a distinctive kind of oversight, but other kinds of learning are a necessary and commonplace strategy for improving the quality of medical care” [6].


There is a surprising lack of guidance for the conduct of ITAs (including highly experimental ITAs) in the context of the German health care system [32]. This is in contrast to various existing guidelines from professional societies and health care organizations in the USA and Canada for the conduct of innovative practice that offer advice for results reporting and documentation practices [17, 18, 33-35]. Furthermore, a rather theoretical ethics framework for innovative care in pediatrics exists [36]. These guidelines could provide indications for developing guidance for the German concept of ITAs. Without systematically derived knowledge about the current practice of ITAs in Germany, however, it might be difficult to develop valuable and context-specific guidelines. It is likely that there is no one-size-fits-all solution. First-in-human ITAs might need guidance other than nonstandard off-label use.

The interviewees had serious concerns about the feasibility of retrospective evaluation. Piloting systematic documentation and evaluation in a subgroup of ITAs would address this concern to a certain extent. The results of this interview study can inform such piloting activities, further research and further patient and stakeholder activities in this regard.

Similar to retrospective evaluation, the need for prospective evaluation might be more fruitfully discussed for different subgroups of ITAs. Relatively strong normative arguments, for example, can be listed for prospectively reviewing ITAs that employ highly experimental, first-in-human therapies. In these cases, it is particularly difficult for physicians to correctly assess the risks and benefits, and conflicts of interest could be more severe [7]. In the USA, an established review practice for the use of experimental drugs outside of clinical research already exists. Within the Expanded Access Program (for individual patients), a positive vote by a research ethics committee and the U.S. regulatory authority, the Food and Drug Administration (FDA), is required [37]. In the context of the debate around the “Right to Try” law, which was introduced nationwide in the USA in 2018, some authors of the "Compassionate Use & Preapproval Access" working group pointed out that a review by the FDA and a research ethics committee is beneficial for patient safety [37-39].

**Strengths:** We are the first to empirically address stakeholders’ attitudes toward the evaluation of ITAs.

**Limitations:** Our sample had a gender imbalance, with an overrepresentation of male interviewees. This was partly due to the gender imbalance in certain positions in the German health care system. Our clinical sample consisted only of physicians working at university medical centers. It is possible that ITAs are also performed in other hospitals or on outpatients. We focused on university medical centers because we assumed that most patients for whom standard therapy has failed would be treated in these contexts. It is possible that people who felt a certain need to evaluate the practice of ITAs were more eager to participate in our interviews. The aim of this study, however, was not to quantify the need for practice evaluation. The aim was to describe the qualitative spectrum of arguments and viewpoints illustrating the strengths and weaknesses of such evaluation activities.

**Conclusions**

More research on the concrete context and subgroups of ITAs and the close collaboration of stakeholders, such as physicians, professional societies, health care organizations and
patients/patient representatives, is necessary to develop a successful evaluation strategy that safeguards the ethically important aspects of the quality and safety of ITAs.
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## Tables

**Table 3**: Retrospective and Prospective Evaluation of ITAs

| RETROSPECTIVE EVALUATION | System responsibility | Knowledge gain about the practice of ITAs | General | Strengths |
|--------------------------|------------------------|------------------------------------------|---------|-----------|
| E1a                      | [Author’s note: It would be good…] if you simply know, what kind of cases exist. You have probably heard of a relatively large number of cases (...) but that is not systematic knowledge about what kind of cases of ITAs exist. (Interview13--edited, Pos. 24) – clinical ethics expert | Data from interviewee | Strengths |
| E1b                      | It is simply interesting from a medical-scientific point of view to get an overview of what is actually being done there [in ITAs – author’s note]. How large is the scope? Which therapies are actually used in the context of ITAs? What is the approval rate? How do the health insurance companies deal with it? How long does it take? (Interview 15--edited, Pos. 12) – neurologist | | |
| E2                       | I believe that it would be generally necessary to better understand the conditions under which ITAs are carried out in general, not in relation to a specific disease, but in general. The practice of individual therapeutic trials could be optimized by considering, for example, what standards have to be met in terms of weighing up the benefits and risks. What special requirements might be placed on informed consent and so on? (Interview 13--edited, Pos. 18) - clinical ethics expert | | |
| E3                       | I could make a very graphic example now. Sometimes I maybe don’t know whether it is an ITA or an off-label use. I think there are many borderline areas, so it would of course be good to have an overview to better categorize what counts as an ITA. (Interview 11--edited, Pos. 13) – interviewee from the level of self-administration | | |
| E4                       | In principle, I see two ethical arguments in favor of this [an evaluation – author's note]. One is that ITAs are usually treatments that are associated with a risk-benefit potential that is much more difficult to calculate. This means that they are ethically more sensitive. (Interview 13--edited, Pos. 18) – clinical ethics expert | | |
| E5a                      | (...) if you had such a registry and could see: Okay, the patient in city X has already been treated with this drug once, so I can call the responsible person and ask how it went. (Interview 2--edited, Pos. 14) – oncologist | | |
| E5b                      | I think, purely in terms of content, (...) it can be helpful to see: Have others used similar substances in a similar indication? What were their experiences? Can I deduce something from this for my patient? Or are there any risks that I perhaps do not know about or have not weighted enough, or vice versa? (...) That’s why I think it would be positive to use others’ experiences. (Interview 15--edited, Pos. 12) – neurologist | | |
| E6                       | You have much more possibilities to argue if you can say, "You can see in the registry data that this drug has already had initial success in the context of an ITA - not | | |
| Weaknesses | Validity and practical relevance of evaluation results |
|------------|-----------------------------------------------------|
| E13        | An ITA is definitely not evidence-based medicine but is at best an attempt to help a patient in an often hopeless situation in oncology. (...) so for me the evidence of an ITA is close to zero. (Interview 19--edited, Pos. 27) – level of self-administration in the health care system |

| Insufficient validity of intervention-specific evaluation |
|-----------------------------------------------------------|
| E13                                                       | An ITA is definitely not evidence-based medicine but is at best an attempt to help a patient in an often hopeless situation in oncology. (...) so for me the evidence of an ITA is close to zero. (Interview 19--edited, Pos. 27) – level of self-administration in the health care system |

| Retrospective evaluation is not a substitute for prospective testing |
|-------------------------------------------------------------|
| E14                                                        | The next big hurdle will be that the retrospectively collected data cannot replace studies. (Interview8.MP3--edited, Pos. 34) – neurologist |

| Results of the evaluation strongly depend on chance and post hoc interpretations |
|----------------------------------------------------------------------------------|
| E15 a                                                                      | But in the end, it's not a thorough study. In the sense that you don't have a homogeneous collective and you only have clinical practice (..), so you can't really isolate and really know what the effect of the drug you used is. (Interview9.MP3--edited, Pos. 40) – physician |

| Knowledge gain about the intervention used |
|---------------------------------------------|
| General                                    |
| E8                                          | I assume that the moment one makes an [assumption – author’s note] from the existing knowledge of medicine that there is justified reason to use certain procedures in a patient with a certain indication, that the more I know about how this has already been tried and with what results, the more precisely the question of the likelihood of success can be assessed. (Interview 16--edited, Pos. 16) – legal expert |

| Need for knowledge gain for rare diseases |
|-------------------------------------------|
| E9                                         | There is an interest, particularly in the area of orphan diseases, in generating evidence. (Interview 12--edited, Pos. 5) – patient representative |

| Learning from failures |
|------------------------|
| E10                     | (...) that not everyone makes the same mistake, simply because they do not know what the results of ITAs were somewhere else in the world. It is precisely the unsuccessful ITAs that are the problem (...) If something works, it is published and can be researched very well, but all the things that do not work are of course not well documented. (Interview 6--edited, Pos. 16) - oncologist |

| Data as a basis for future studies |
|-----------------------------------|
| E11                               | (...) if certain ITAs prove to be particularly promising (...) this should naturally be taken as an occasion to develop a research question from it. (Interview 16--edited, Pos. 28) – legal expert |

| Potential basis for approval |
|------------------------------|
| E12 a                        | That's what it's really about, (...) to collect and provide data that are clinically plausible in order to expand the spectrum of indications. (Interview8.MP3--edited, Pos. 34) – neurologist |
| E12 b                        | (...)If you set up such a registry in a sensible way, that could be the basis for getting approval in general. Because there are sometimes approvals based on phase II studies, but some diseases don't allow large phase III studies to be set up. Like this, the data could be used a little bit more for the benefit of other people. (Interview 2--edited, Pos. 14) – oncologist |

| Development of evaluation strategies for personalized therapies |
|---------------------------------------------------------------|
| E7                                                           | An evaluation would be useful because we're actually going to get more and more individualized therapies, and we need to develop appropriate evaluation tools for how to evaluate therapies that are specific to fewer and fewer patients. (Interview 13--edited, Pos. 22) – clinical ethics expert |

| as a study, but there are at least already indications that it often does work or seems to work* (Interview 1--edited, Pos. 14) – oncologist |

*Interview 1--edited, Pos. 14
*Interview 8--edited, Pos. 34
*Interview 16--edited, Pos. 28
*Interview 19--edited, Pos. 27
*Interview 2--edited, Pos. 14
*Interview 6--edited, Pos. 16
*Interview 10--edited, Pos. 16
*Interview 12--edited, Pos. 5
*Interview 13--edited, Pos. 22
*Interview 14--edited, Pos. 16
*Interview 15--edited, Pos. 40
*Interview 16--edited, Pos. 28
*Interview 18--edited, Pos. 22
*Interview 19--edited, Pos. 27
*Interview 20--edited, Pos. 26
*Interview 21--edited, Pos. 23
*Interview 22--edited, Pos. 25

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| Code | Description |
|------|-------------|
| E15  | in nuclear medicine |
|      | You would need explicit ideas beforehand about what the adverse effect could be and how to distinguish it from anything that happens in the context of this disease process anyway. (Interview 11--edited, Pos. 9) - level of self-administration in the health care system |
| E16  | Strongly limited generalizability of the evaluation results |
| a    | The other question is whether I can gain knowledge in this area in a systematic way that will allow me to make any additional statements afterward, or whether it is just a topic where this is not possible. (Interview 11--edited, Pos. 7) - level of self-administration in the health care system |
| b    | How individual is the individual treatment attempt and can we draw conclusions from it, which would mean that I can draw them on a more abstract level. (...) can we then make such a generalization that one could derive anything from it? (Interview 11--edited, Pos. 17) - level of self-administration in the health care system |
| c    | If I now have an intensive care patient who is severely ill with COVID, then he does have COVID, but an intensive care patient usually also has a bunch of catheters somewhere, possibly needs circulatory support, possibly loses his kidney function, then has superinfections through the catheters or through something else. Then, I might have the constellation that I have an inflammatory syndrome here, I can't detect a bacterium, I have coinfection parameters, correspondingly high leukocytes and some other values that are conspicuous and I would assume I have an inflammatory syndrome. If I now start to give some immunomodulatory drug, (...) even though this has no basis, but I say, in analogy to an inflammatory syndrome in some rheumatoid disease, I would now give a rheumatic-modulatory drug. Then, the patients usually have at the same time, because they have high infection parameters and because you can of course never exclude an infection, still an antibiotic. Then, they may have a few copies of some virus somewhere as colonization or infection, which we don't know, and possibly an antiviral drug. They get their cortisone, they have their circulatory support therapy, they get kidney replacement procedures and such stories, so that I find it much more difficult to determine what really happened due to my medication (...) so with the medications that I have seen - it was often not comprehendible what works and what does not work. (Interview 4--edited, Pos. 22) – physician in intensive care medicine |
| E17  | Risk of false conclusions (in the case of intervention-specific evaluation) |
|      | However, other associations say that the data collection can probably lead to wrong conclusions, because the ITAs are so individual that it is not possible to evaluate them clearly and precisely. (Interview 4--edited, Pos. 22) – physician in intensive care medicine |
| E18  | Interference with therapeutic freedom |
|      | Only nonclinicians mentioned this code. |
| E19  | Difficult distinction between ITAs and research |
|      | You can certainly do that [an evaluation - note A.F.] - it is just a fine line between an ITA and large-scale research. (Interview 4--edited, Pos. 16) - physician in intensive care medicine |
| evaluation results can be a disappointment for patients | intensive care medicine |
|--------------------------------------------------------|-------------------------|
| E20 | I'll start at the psychological level. It can lead to disappointment. So that I'm aware that something obviously doesn't work, that I've spent a lot of money on, or that I've invested a lot of hope in. (Interview 18--edited, Pos. 20) – patient representative |

### Strategies for Evaluation

| evaluation goal | Non-intervention specific |
|-----------------|----------------------------|
| E21 a | One would be to register and evaluate ITAs in general, that means not specifically for a certain disease or a certain therapy, but in general. That would be a sensible way to evaluate them. (Interview 13--edited, Pos. 8) – clinical ethics expert |
| E21 b | Although I think I could even imagine that you simply say that you would like to do a descriptive collection first. How often is that [an ITA – author’s note] used at all? Or simply that if you just collect free ITA, yes or no, something like that. And in which indication? And then - detached from the specific drug and the specific patient case. (Interview 15--edited, Pos. 20) – neurologist |

| intervention-specific | Qualitative evaluation |
|-----------------------|------------------------|
| E22 a | The other option [for evaluation - note A.F.] will become particularly relevant for gene-based therapies, which are suitable for fewer and fewer patients. It would of course make sense, if such a therapy is used in individual cases, to aggregate and evaluate the data across different comparable therapies. (...) This would be disease-related or related to the mechanism of action and not on the other superordinate level (...). (Interview 13--edited, Pos. 8-9) – clinical ethics expert |
| E22 b | I would like a low-threshold accessible exchange possibility: Who has already used what in my field and what experience has been had with it? I think that would be helpful for individual decisions. (Interview 15--edited, Pos. 16) – neurologist |

| evaluation method | Registry |
|-------------------|----------|
| E23 a | What are appropriate forms of evaluation? (...) but I could imagine - I don't know if the cases are not too different - that one could try, perhaps also qualitatively, to research this more systematically. (Interview 13--edited, Pos. 66) – clinical ethics expert |
| E23 b | If one pursues this sociological medical-ethical research program, one could, for example conduct participatory field studies in a setting where ITAs take place frequently. (...) One could do ethnographic research. One could then try to inquire or find out directly on the spot: How did it come about that this senior physician has now suggested the ITA? (Interview 20--edited, Pos. 16) – bioethicist |
| E24 | One could require a legal obligation for detailed documentation in a prospective registry for the conduct of an ITA. As a condition for the conduct of an ITA. (Interview9.MP3--edited, Pos. 60) – physician in nuclear medicine |

| threats | resource scarcity | documentation completeness |
|---------|-------------------|---------------------------|
| E25 | For us, the bottleneck is always the completeness of the documentation. (...) This inconsistency of documentation is one of the difficulties when you want to evaluate something like this [an ITA – author’s note]. (Interview 6--edited, Pos. 10) – oncologist |
| Topic                                    | Quote                                                                                                                                                                                                 | Source                                                                 |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Bureaucratic obstacles                  | Perhaps also bureaucratic obstacles, simply that one sets up something like that [an evaluation — author's note] at all and then that one thinks of adding someone to such a database. (Interview 2—edited, Pos. 20) — oncologist | oncologist                                                           |
| Financing (Registry)                    | It's also simply a question of costs: Who administers this register? Who pays the people who work on it? Are they people who sit on some third-party contracts, time-bound research projects? Or are they permanent employees who don't have to help finance their own office chairs? (Interview 1—edited, Pos. 18) — oncologist | oncologist                                                           |
| Workload for data collection            | What is of course a fundamental problem is the effort. The effort for those involved. The question now is whether it would be ethically appropriate, for example, to create a registry for ITAs, which would perhaps be the most extensive form of evaluation. Of course, that would possibly involve a considerable amount of work. These would be rather pragmatic reasons, where one then has to weigh up, Is this effort justified regarding to the expected knowledge gain? (Interview 13—edited, Pos. 28) — clinical ethics expert | oncologist                                                           |
| Conflicts of interest when conducting an evaluation | One problem with these registries are conflicts of interest. Who has access to them? Who also has sovereignty over the evaluation of the data? Who actually determines what happens to this data? And each of the parties involved has conflicts of interest - the pharmaceutical manufacturers want to sell their products, the researchers want to publish the most spectacular things possible, and the health insurance companies want to save as much money as possible. (Interview 1—edited, Pos. 20) — oncologist | oncologist                                                           |
| Career interests                        | And the other thing is that different individuals also have individual interests, for example to publish particularly individually interesting cases, and they might not necessarily be willing to share the data before they have published them. (Interview 15—edited, Pos. 16) — neurologist | neurologist                                                           |
| Legal risks for physicians              | I think that this also has something to do with legal issues. Because the moment I say, I'm now making an ITA in the hope of helping, because I know that everything else hasn't helped so far, and then that doesn't work either, there's also the fear that by documenting a failure, you're putting yourself in a liability position where you ask yourself, do I possibly have to justify myself at some point on the basis of the facts that I've documented? For not having, for example, looked at certain information actually available in the world beforehand? And am I not raising the threshold for acting in the patient's best interests by simply saying, "What is actually the standard of prior inquiries or medical knowledge required of me that I must have in order to really be allowed to assume that the course of action that I specifically then choose can still be regarded as promising?" (Interview 16—edited, Pos. 18) — legal expert | legal expert                                                          |
| Data protection                         | The main problem is of course as always data protection. (Interview 17—edited, Pos. 15) — person from a health insurance company                                                                                       | person from a health insurance company                                |
| Pretext for money saving measures for health insurance companies | On the other hand, one does not want to create a situation where colleagues publish or document unsuccessful ITAs even in individual cases, which | person from a health insurance company                                |
| Opportunities | Stakeholders involved in the evaluation | Participation in the design and conduct of the evaluation | Possession and control of a registry | Pediatrics: difficulties physician-parents relationship | Stakeholder’s interest | Time capacity | Monetary incentive for documentation | Automated documentation | Obligation as an incentive for documentation |
|---------------|----------------------------------------|---------------------------------------------------------|----------------------------------|---------------------------------------------|------------------------|--------------|------------------------------------|--------------------------|----------------------------------------|
|               | [E34] There is another problematic aspect: how and who runs this registry? (Interview 1--edited, Pos. 14) – oncologist |   | [E34] Possession and control of a registry | [E35] Whether drugs are approved or not doesn’t matter to most parents. They say "Just do it. You know that we trust you." I can imagine that if this [the uncertainty regarding the risk-benefit ratio of the drugs used – author’s note] is discussed more in everyday work, it will also make it more difficult to work with parents in general. Of course, it’s also an ethical question to what extent this is addressed or not. But I believe that if this is discussed more in everyday clinical work - even if it’s only for one drug - it will also be discussed more with the parents and possibly make the work more difficult. (Interview 14--edited, Pos. 29) – pediatrician | [E36] If the aim were to promote ethically responsible practice in an area where the physician’s individual scope for reflection and decision-making is so important, it would be particularly important to involve these groups in the sense of participatory research in the generation of possible approaches to solutions [for an evaluation – author’s note]. (Interview 13--edited, Pos. 66) – clinical ethics expert | [E37] Well, that would be based on gut feeling, but I think that you would have to start with people who have fun and are interested in this topic [of evaluation - note A.F.] as part of a research project. (Interview 11--edited, Pos. 58) – level of self-administration in the health care system | [E38] If you had such an extra time window where you could somehow do such research [as a physician to search for similar ITAs -A.F. note]. (Interview 2--edited, Pos. 22) – oncologist | [E39] My experience is, as long as you don’t link the salary [of, e.g., the physicians – author’s note] to the documentation requirement, it doesn’t happen with sufficient consistency. The only effective way to achieve 100% documentation is to link it to the salary. (Interview 17--edited, Pos. 50) - person from a health insurance company | [E40] The first question would be whether such a process could not be automated. (...)If these data about the therapy, about the proposal [for reimbursement – author’s note], about the patient, about his pre-existing conditions, about the additional medications, about the lines of therapy he has already had. (...)If all these already available data were to flow into the registry in an anonymized, pseudonymized version, that would certainly be the ideal thing for everyone involved. (Interview 1--edited, Pos. 16) – oncologist | [E41] I think it’s a mixture of: You have to enact it [documentation – author’s note] to get it off the ground, and then people have to realize what the added value is. (Interview 6--edited, Pos. 20) – oncologist |
Additional personal for documentation

E42

I think it must be and it will be the approach in such situations in the future, that there is someone professionalized for this [documentation – author’s note], who exclusively does this and who can do it much better than the physicians. (Interview 1--edited, Pos. 20) – oncologist

Structural factors

Patients open for data use

E43

It almost never happens that a patient says, “No, I don’t want my data to be scientifically analyzed. I have always explained this to the patients, and I can’t remember a single case where the patient said, “No, I don’t want that.” The cooperation of the patients is there, that’s not the problem. (Interview 17--edited, Pos. 50) - person from a health insurance company

Finding areas where ITAs are often conducted

E44

I would try to find out beforehand in which areas this [ITAs – author’s note] is particularly common. (Interview 11--edited, Pos. 62) – level of self –administration in the health care system

Distinction of ITAs from research is legally unproblematic

E45

Simply documenting what you have done in a particular single case does not change the purpose of what you did. That is, I can certainly say: “I have recognized that the previous treatment alternatives for these patients are not promising or have even already failed. I have tried something new, where I had the justified hope that it could bring a treatment success, independently form the occurrence of the treatment success. I try to just document, like in the protocol of an experiment, what I did.” And then to throw that into a pool that is evaluable for the professional world, I don’t consider that at all to be overstepping the boundaries in the direction of the goal of gaining knowledge. I really just consider it a subsequent documentation of something that didn’t have the primary purpose or even the secondary purpose of gaining knowledge. It can be completely distinguished from the question of intent, (there again the jurist speaks.) With the ITA, I might have the attempt to say: “To the best of my knowledge and belief, I am doing the best I can to cure this patient, who otherwise has no chance”. (Interview 16--edited, Pos. 12) – legal expert

PROSPECTIVE EVALUATION (Review)

Strengths

Support of rational risk-benefit assessment

R1

There is an enormous emotional relationship when you have treated a patient for a long time. The [relationship – note A.F.] is not only characterized by scientific considerations (...) However, I think it makes a lot of sense to involve someone who does not treat the patient himself and does not have this emotional connection, because this then puts the whole thing in a somewhat more objective and scientific context, which is not influenced by these emotional relationships. (Interview 17--edited, Pos. 44) - person from a health insurance company

Good practice for safeguarding favorable a risk-benefit-ratios

R2

Yes, I think it is important to really check again whether the assessment [of the risk-benefit analysis – author’s note] is correct. (...) The assessment must really be good. What are the opportunities? What are the risks? Is it justifiable if I suggest this to the person? Well, because I then give hope (...) (Interview 2--edited, Pos. 28) – oncologist
| Weaknesses | Strategies for review |
|------------|----------------------|
| Interference in physician's work | Interdisciplinary board |
| Interference in physician's sphere of competence | Difficult to standardize/Need for a case related review |
| R3a | R8a |
| R3b | R8b |
| It has to be said that there is a risk that the person making the request [for a review – author's note] may feel that his competence has been curtailed in some way and that he has been put out a bit. (Interview 7--edited, Pos. 18) – clinical ethics expert |
| An interdisciplinary team (...) where you discuss together what the possibilities are and then jointly make this suggestion to the patient. (Interview 2--edited, Pos. 28) – oncologist |
| Some people will be uncomfortable with the fact that they can no longer just freely say, "Yes it's my responsibility, and I decide with whom I do it [the ITA – author's note]. Actually, it is my therapeutic freedom." (Interview 9.MP3--edited, Pos. 72) – physician in nuclear medicine |
| However, an interdisciplinary "board" decision as a basis for an ITA is certainly a reasonable and feasible way to go. (Interview 10--edited, Pos. 56) – physician in nuclear medicine |
| R4a | Context-specific review/strategy depends on further variables |
| I believe that it is also important for the physician–patient relationship, for the trust that patients have in their physicians, that they just assume, "Here sits this individual in front of me, and behind him or her, there is not another faceless committee that decides my fate". (Interview 1--edited, Pos. 22) – oncologist |
| (...) and that is possibly a deeply established physician–patient relationship. Of course, I always introduce a certain disturbance when I involve a second person. (...) That has possible advantages but also possible disadvantages. I think you have to weigh that up against each other at this point. (Interview 11--edited, Pos. 72) – level of self-administration in the health care system |
| R4b | R7 |
| Endangering trust in the physician–patient relationship | (...) depending on who conducts the ITA. I do believe that there are differences in the quality of therapy depending on the area. For example, in oncology there are units where you are well cared for, where you get good information about what can still be achieved and what cannot be achieved. And there, possibly, the effect of a second opinion or a 4-eyes principle would not be very high. Now, if I knew that 75 percent of all ITAs are not provided right there, that would influence my answer. I don't even know where the ITAs are conducted. (Interview 11--edited, Pos. 64) – level of self-administration in the health care system |
| R5 | |
| I think that the individual decision of each physician on site - which patient benefits from which drug - is a very important part of care. In the future, we will need people who want to do this job. And it creates discord if you always have a committee where you first have to get permission for what you do. (Interview 1--edited, Pos. 22) – oncologist |
| R6 | |
| This cannot be standardized, but I believe that this is part of the individual decision. So if the doctor says, my competence as a respective specialist comes to a limit, I may have to bring in another specialist from another discipline to understand it sufficiently well or to be able to assess it with sufficient certainty, then yes [a review is needed – author's note]. (Interview 3--edited, Pos. 33) – clinical ethics expert |
| R7 | |
| (...)=depending on who conducts the ITA. I do believe that there are differences in the quality of therapy depending on the area. For example, in oncology there are units where you are well cared for, where you get good information about what can still be achieved and what cannot be achieved. And there, possibly, the effect of a second opinion or a 4-eyes principle would not be very high. Now, if I knew that 75 percent of all ITAs are not provided right there, that would influence my answer. I don't even know where the ITAs are conducted. (Interview 11--edited, Pos. 64) – level of self-administration in the health care system |
Demand for ethical expertise

In our case, ethical expertise happened to be in on it, but it is not really institutionalized. (...) But that would certainly be something desirable. (Interview 6--edited, Pos. 32) – oncologist

Maybe even the local research ethics committee should be made responsible for the supervision of ITAs to assure that certain ethical principles are followed. (Interview9.MP3--edited, Pos. 62) – physician in nuclear medicine

Unsure about a review strategy

It would certainly be helpful if there were some form of consultation so that you could get a second medical opinion in some form. But I think it’s rather problematic to always take an official path, that a second opinion should always be obtained. (Interview 12--edited, Pos. 26) – patient representative

No review needed

I am rather skeptical about the benefits of ethics committees. I think that the individual decision of each physician on site - which patient benefits from which drug - is a very important part of care. (Interview 1--edited, Pos. 22) – oncologist

Resource scarcity

I'm not sure if the disadvantages outweigh the benefits: That [the review - note A.F.] could become a paper monster. A control mechanism is introduced and then it gets automatically out of hand after two or three years. (Interview 10--edited, Pos. 14) – physician in nuclear medicine

Lack of time

Of course, it would be important that they [a review board – author's note] meet regularly; something weekly would be needed (...) because patients do not have much time [in the context of an ITA – author’s note]. A board that meets every quarter would not be a good instrument. (Interview 6--edited, Pos. 30) – oncologist

Criteria for choosing the form of review

We would have to think again about how to create a system where an ethical review is possible and also practicable and where we perhaps also develop criteria for when this [the review - note A.F.] is necessary and when it is not. (Interview 13--edited, Pos. 49) – clinical ethics expert

Collegial atmosphere

Most of the time, the relationship or the coordination in our tumor board is very collegial. If I have thought about a patient, I present it to the tumor board, and it never actually happens that someone says: "No, I think that's totally stupid. You shouldn't do that." Because most of the people in the tumor board want to make decisions in the patient’s best interest, and of course no one would say, "No, you shouldn't do that." If someone has already thought more about it, then they are usually listened to... (Interview 2--edited, Pos. 36) – oncologist

* For better comprehensibility, we have slightly adjusted the grammar of the quotes and omitted filler words as well as repetitions.

Table 4*: Categories of ITAs
### Setting Individual treatment attempts (ITAs)

| Types/Categories | Off-label use | S1a | S1b | S1c |
|------------------|---------------|-----|-----|-----|
|                   |               | The situation in the intensive care unit, I am in the COVID intensive care unit, is that, as expected, nothing is approved for COVID after one year apart from dexamethasone and Clexane. That is, all immunomodulatory drugs that could be applied are administered in the sense of an individual remedy trial. Patients sign a sheet upon admission. In it, we inform the patients that if certain laboratory constellations or certain clinical constellations occur during the course of the disease that suggest an inflammatory syndrome associated with COVID, we would in that case carry out immunomodulation with substances that are not approved for COVID but are approved for various other diseases. (Interview 4--edited, Pos. 10) – physician in intensive care medicine |
|                   |               | We have a focus in “city” with minimally invasive epilepsy surgery, and that includes deep brain stimulation and stereotactic laser thermocoagulation. Deep brain stimulation is actually formally approved for one target point, and we have a second one, and we know that it is supposed to be at least as good. There is a constellation of patients for whom we have applied for an ITA more often, either because they were children or people with mental disabilities or because, for example, this target point that we want to reach with deep brain stimulation is no longer available because the patients have brain damage. That's our business, so to speak, that we have to do something like that outside of the formal indication. (Interview8.MP3--edited, Pos. 2) – neurologist |
|                   |               | (...) these activities in these programs often result in the discovery of 'targets' that result in 'off-label use'. 'Drug repurposing' plays a large role or is actually the most common outcome of very broad genetic analyses. So, very specifically, a whole genome and RNA analysis in a young patient with an out-treated malignancy, to whom we have nothing to offer in standard therapy, results in a discussion in the molecular tumor board, and there the most frequent 'outcome' is that we recommend a 'repurposing' or a 'repositioning' of an approved substance, (...) in the context of ITAs, a relatively large amount of immunotherapy is done, certainly also outside the label, especially in younger patients who are still in a good condition, for whom one does not want to give up. (Interview 6--edited, Pos. 2) – oncologist |
| No approval in the EU or in general | S2a | Basically, it is like this: In oncology, we have above all the setting of chemotherapies that are not yet approved in Germany or in Europe, or rather targeted therapies for certain tumor entities. Either the substance (...) has not yet been approved (...) or we apply to the respective health insurance company for reimbursement of the costs of this drug for a specific patient. In the vast majority of cases, these are seriously ill patients who have already undergone many lines of therapy and where a progression of the disease was nevertheless recorded under the last line. (...) Exactly, so really this individual trial of a drug that is not approved at all, that is exactly in this setting. (Interview 1--edited, Pos. 2) – oncologist |
|                   |               | Individual treatment attempts. There are two types and categories. On the one hand, there are the nonapproved, nonestablished procedures (...). (Interview9.MP3--edited, Pos. 12) – physician in nuclear medicine |
| Completely experimental, "from bench to bedside" | S3 | Now, in the case of completely experimental things, i.e., when you say that someone has a high probability, based on the tumor profile, that you could achieve something with something completely new that is still fresh from the laboratory, which is already being tried at the center once or twice - of course you cannot submit that to the insurance company - and that is then ultimately something that the hospital pays for. (Interview 4--edited,
Pos. 6) – physician in intensive care/oncologist

* For better comprehensibility, we have slightly adjusted the grammar of the quotes and omitted filler words as well as repetitions.