ThemenCheck Medizin

Extract of HTA report

Contraception[1]

Comparison of hormonal IUD and copper IUD

Health technology assessment commissioned by IQWiG

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IQWiG coordinated the project and conducted the literature search for the domains "Benefit assessment" and "Health economic evaluation" and prepared the easily understandable summary ("HTA kompakt").

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According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A11 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

Insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies through "ThemenCheck Medizin" (Topic Check Medicine) to the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). The assessment is done in the form of a Health Technology Assessment (HTA) report. HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 new topics are selected each year from among all submitted proposals. According to the legal mandate, these topics are supposed to be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In the summer of 2021, IQWiG commissioned a team of scientists led by SHARE TO CARE to work on the selected topic "HT21-05: Contraception: comparison of hormonal IUDs and copper IUDs". The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal, and organizational topics as well as a gynaecologist.

Why is the HTA report important?

The results of a survey conducted by the Federal Centre for Health Education in 2018 show that after oral contraceptives and condoms, IUDs are the third most commonly used contraceptive method in Germany. They are used by about 10% of sexually active women. The proportion is higher, at 20%, in women aged 40 to 49 and lower, at 5%, in women aged 18 to 29 [2,3].

Two different forms of IUDs are predominantly used for contraceptive purposes: hormonal IUDs and copper IUDs. Both types of IUDs are inserted into the uterus by a gynaecologist following a gynaecological examination. Removal is also carried out by a gynaecologist. Depending on the model, hormone IUDs must be replaced after a maximum of 6 years and copper IUDs after 5 years. Additionally, it is recommended to undergo regular ultrasound checks to ensure proper positioning of the IUD.

Hormonal IUDs consist of a T-shaped plastic body and a hormone reservoir. In the uterus, the IUD consistently releases small amounts of hormone (levonorgestrel) and prevents the

implantation of a fertilised egg in the lining of the uterus from the moment of insertion. Copper IUDs consist of a T-shaped or anchor-shaped plastic body wrapped with a copper wire. Copper ions have a spermicidal effect. In addition, copper IUDs make it more difficult for a fertilised egg to implant. Advancements of the copper coil, e.g. copper chains and copper balls, are also on the market. While these advancements share the same principle of action, different or more flexible shapes are intended to prevent expulsion of the IUD or potential damage to the uterus.

In addition to IUDs, a number of well-known and lesser-known methods to protect against unwanted pregnancy exist. It is important to choose a method that fits the respective life circumstances of the persons concerned. According to the German Federal Centre for Health Education, the ideal contraceptive would be, among other things, "absolutely safe and reliable, free of side effects, easy to discontinue and without lasting effects on fertility. It would be equally applicable for women and men, inexpensive, easy to use, would not interfere with sexual intercourse, and could also be used easily by people with disabilities" [4]. Since this ideal contraceptive does not exist to this day, it is important to analyse the advantages and disadvantages of contraceptives. Therefore, a member of the public suggested comparing hormonal and copper IUDs: How safe are these contraceptives? What are their respective positive and negative side effects? And how are these positive and negative side effects experienced and evaluated by their users?

Objective of the HTA report

In light of the interest of the person proposing the topic, the commissioned team of experts compared hormonal versus copper IUDs from the different perspectives of an HTA report. In addition to contraceptive reliability, the report focuses on the question of how the 2 types of IUDs compare in terms of their positive and negative side effects, e.g. pain or effects on menstruation.

Which questions are answered – and which are not?

Benefit assessment

The team of scientists evaluated 8 studies comparing hormonal and copper IUDs. The 3 largest included studies were multicentre and international and had between 2246 and 3836 participants. Overall, the number of participants in all studies ranged from 140 to 3836 (median: 516.5). The follow-up time ranged from 3 months to 10 years and was longest in the 3 largest studies at 5, 7, and 10 years. In addition to results on the safety of the 2 types of IUDs, the studies contain numerous results on various positive and negative side effects. However, none of the comparisons found included newer systems such as copper chains or copper balls.

All studies show that both copper IUDs and hormonal IUDs reliably prevent pregnancies, with hormonal IUDs performing slightly better than copper IUDs.

It was also found that hormonal IUDs were more likely to stop menstruation than copper IUDs. Heavier menstrual bleeding, on the other hand, occurs more often in women using copper IUDs. Although the hormone quantity released by hormonal IUDs is very small, women who use hormonal IUDs may experience hormone-related symptoms such as acne, nausea, depression, or weight changes.

In addition, both IUD types are associated with side effects such as pain, infection, or IUD slipping or accidental loss. With regard to these outcomes, however, the authors of the report found no significant differences between the 2 types of IUDs.

For the outcome group "health-related quality of life", i.e. the subjective summary experience of health-related advantages and disadvantages, no difference was found regarding any of the measured dimensions.

When interpreting the results, it should be noted that all studies suffered from methodological shortcomings: For example, in most cases, both study participants and treatment providers knew who had received a hormonal IUD or copper IUD. This knowledge may influence how often certain concomitant or side effects were perceived by participants, documented, and reported in the studies.

Health economic assessment

The HTA report has found that the total 5-year costs including follow-up examinations and removal range from €300 to €850 for a hormonal IUD and from €200 to €750 for a copper IUD. For copper-containing systems, it should be noted that the costs of simple copper IUDs tend to be at the lower end, while those of newer systems (e.g. copper balls) tend to be at the upper end of the reported range. The costs for an IUD are covered by the statutory health insurance (SHI) for women of childbearing age under 22 years, except for an annual co-payment of about €15 to €35. The coverage of costs for women under 22 years of age also applies to other contraceptives such as the oral contraceptive pill. Women aged 22 years or older must cover almost the entire costs out of pocket.

The authors were able to identify 2 health economic studies which examine the cost-effectiveness of different contraceptives. The analysis showed that both hormonal and copper IUDs are cost-effective compared to other contraceptive methods such as the oral contraceptive pill or condoms. According to the authors of the report, this is due in particular to the long duration of use and the comparatively high effectiveness of IUDs. However, the bulk of the cost of contraception with an IUD is front-loaded (cost of the IUD itself and cost of

insertion), whereas the cost of methods such as the oral contraceptive pill is distributed evenly over the entire period of use.

Further aspects

Users of both types of IUDs favourably mention the long-term action of these contraceptives and the feeling of safety they create. However, women may perceive the side effects of contraception with an IUD very differently. For example, the absence of menstrual bleeding as a possible side effect of hormonal IUDs is perceived positively by some women, while others experience it as frightening and unnatural.

The authors of the report therefore emphasise that the decision in favour of a contraceptive method, and thus also the decision in favour of a certain type of IUD, depends on user preferences. It is therefore important to provide interested users with comprehensive information, including about positive and negative side effects. This could help avoid situations where the occurrence of unanticipated side effects leads to premature removal of the IUD.

In the analysis of ethical aspects, the focus was on the question of autonomy as in self-determined decision-making. In this regard, there were no differences between copper and hormonal IUDs.

What's the next step?

This report comprehensively summarises the available results from studies comparing hormonal versus copper IUDs. It shows that the 2 contraceptive methods differ, especially with regard to their effects on menstruation, but that both are safe and cost-effective contraceptive methods. It would be desirable to have more information on advancements of copper IUDs, e.g. copper chains or copper balls.

The results of the HTA report can be used to inform women interested in IUD contraception about its effectiveness as well as positive and negative side effects. For instance, information for interested parties can be created or further developed on the basis of the present HTA report. The results of the HTA report are also presented in a generally understandable way in "ThemenCheck kompakt", which was published on IQWiG's website at the same time as the report.

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HTA key statements

Research questions of the HTA report

The aims of this investigation are to

- assess the benefit of contraception with copper intra-uterine devices (IUDs) compared to hormonal IUDs in women of childbearing age with a desire or indication for contraception with regard to patient-relevant outcomes. The focus of the assessment is on whether the 2 types of IUDs differ in terms of their positive and negative side effects.

- determine the costs (intervention costs) and assess the cost-effectiveness of contraception with copper IUDs compared to hormonal IUDs

- review ethical, social, legal, and organizational aspects associated with the medical intervention.

Conclusion of the HTA report

The research question of the present health technology assessment (HTA) report firstly called for an investigation of the benefits of contraception with copper IUDs versus hormonal IUDs in women of childbearing age with a desire or indication for contraception. The focus was on whether the 2 types of IUDs differ in terms of their positive and negative side effects. Further research questions of this report involved the calculation of costs and the evaluation of the cost-effectiveness of contraception with copper IUDs versus hormonal IUDs as well as the review of ethical, social, legal, and organisational aspects associated with the medical interventions.

For this research question, a total of 33 outcomes from 8 randomised controlled trials were assessed and combined into 7 outcome groups. For the outcome group "pregnancy and expulsion" (4 outcomes), a hint of a minor advantage of hormonal IUDs was found regarding the outcome "pregnancies (all)", although both types of IUDs exhibited high contraceptive effectiveness. In the outcome group "effects on menstruation" (6 outcomes), a hint of less frequent occurrence of various bleeding changes was found for copper IUDs (outcomes: "amenorrhoea" and "hypomenorrhoea"). For the outcome "increased menstruation" (hypermenorrhoea or menorrhagia), a hint of more frequent occurrence with copper IUDs was found. In the outcome group "pain", no differences were found regarding the 3 individual outcomes. In the group "inflammations and other complaints" containing 3 individual outcomes, only the outcome "other complaints" showed a hint of less frequent occurrence in copper IUDs. The outcome group "reasons for removal" combined 8 individual outcomes. One

("other, non-IUD-related reasons") showed a hint of less frequent removal of copper IUDs. For the outcome group "health-related quality of life", no difference was found regarding any of the measured dimensions. In addition, results were extracted on 8 outcomes presented as supplementary information, but no conclusions on benefit were derived from them.

All 8 included studies suffer from a high risk of bias due to lack of blinding and some other methodological deficiencies. In addition, all of the hormonal IUDs used in the studies contained 52 mg levonorgestrel, and most of the employed copper IUDs had a surface area of 300 mm2. Thus, the conclusions of the report are not fully transferable to further developments of the IUDs. Furthermore, the transferability of the available results to younger women (< 18 years) or older women (> 40 years) or to women who have not yet given birth is unclear.

In the foreseeable future, no further studies which might provide relevant results comparing the IUDs or their advancements are expected.

According to the calculations in this report, the total 5-year costs range between €300 and €850 for a hormonal IUD and between €200 and €750 for a copper IUD (see Section 6.1). These estimates include follow-up examinations and IUD removal. The actual costs within the mentioned ranges depend on the price of the respective IUD, the billing modalities (especially Uniform Value Scale versus the German Fee Schedule for Physicians [GOÄ]), and the age and individual situation of the respective patient. The majority of the costs are generally reimbursed by SHI, provided a woman is younger than 22 years. Women aged 22 years or older must cover almost the entire cost out of pocket.

The cost-effectiveness analysis for both types of IUDs shows them to be cost-effective compared to other contraceptive methods. This is due in particular to their long and comparatively high effectiveness. In the reviewed US and UK models, copper IUDs were typically the most cost-effective contraceptive method or at least among the most cost-effective methods. Hormonal IUDs were slightly more expensive, but also slightly more effective, and therefore also cost-effective. For Germany, the 2 types of IUDs presumably likewise represent comparatively cost-effective contraceptive methods, especially compared to no contraception, condoms, or oral contraceptive pills.

The costs of intrauterine contraceptive methods are mainly incurred directly at insertion. However, they then protect the woman for several years. In contrast, the costs of other contraceptive methods, especially oral contraceptive pills, are spread across quarters or the entire year and therefore do not require as high of an immediate expenditure. This might mean that especially younger women or those who are socioeconomically worse off are more likely to spontaneously opt for a short-term method rather than a long-term one. On the other hand, modelling has shown IUDs to be very cost-effective compared to other contraceptive

methods. From an economic point of view, they are therefore a cost-effective alternative both for SHI and for women as self-payers.

The analysis of ethical aspects associated with the 2 types of medical interventions focused on the different positive and negative side effects based on the results from the benefit assessment as well as the determination of costs and the evaluation of cost-effectiveness. The focus here was on their impact on autonomy in the sense of self-determined decision-making in the choice between copper and hormonal IUDs.

Both types of IUDs are suitable for ensuring long-term birth control based on a self-determined decision. In this way, they have an equally (reproductive) autonomy-promoting effect. Both types of IUDs are also associated with aspects which may limit reproductive autonomy. For example, women may delay the insertion or removal of the IUD because of external influences, fear of pain, or the associated costs. Such aspects may limit the free will to initiate or continue long-term contraception and thus birth control.

Particularly the different positive and negative side effects mean that the decision in favour of a copper or hormonal IUD is preference sensitive. Making a self-determined decision requires that the necessary information about the types of IUDs is available. Lack of information may, for instance, lead to a woman having an IUD removed prematurely because of false expectations. In this case, 2 invasive procedures, possibly involving pain, are conducted which could have been avoided. Self-determined decision-making requires comprehensive information and counselling on the expected benefits as well as on positive and negative side effects.

When analysing the social aspects associated with the medical interventions, questions about access and affordability of these contraceptive methods may be extracted from the identified literature. The identified publications consistently indicate that the decision in favour of a contraceptive method is highly dependent on social and cultural norms and values as well as individual life circumstances and preferences ("preference-sensitive decision"). The survey of affected women also suggests that women perceive and evaluate particularly the bleeding-related positive and negative side effects of IUDs very differently. For example, some women welcome the decrease or absence of menstruation, while others experience it as frightening and unnatural.

For these reasons, it is necessary to inform women and couples in a comprehensive, understandable, and balanced way about the benefits and positive and negative side effects of all available contraceptive methods in order to enable "woman-centred contraception" in the sense of shared decision making.

With regard to the legal aspects associated with the medical interventions, hormonal IUDs are medicinal products, whereas copper IUDs are medical devices. In this respect, different procedural standards apply to the approval of these IUDs. In the case of a defective IUD, this results in different bases for women's claims for compensation.

The 2 types of IUDs do not differ in terms of the conclusion of the treatment contract, patient information, or consent to the intervention.

The fact that the costs for both IUD types are reimbursed by SHI funds up to the age of 22 years and are then self-pay is based on social legislation.

Conclusion in terms of addressing the concerns of those proposing the topic:

Overall, this HTA report demonstrates that hormonal IUDs and copper IUDs are comparatively highly reliable and long-acting contraceptive methods that differ only slightly in terms of their effectiveness in preventing pregnancy and their positive and negative side effects. How these differences are evaluated depends on the respective woman’s values and preferences and her situation in life. Since the choice of contraceptive is a preference-sensitive decision, it is necessary to provide complete information which covers all contraceptive methods, is correct in terms of content, and is comprehensible for the general public. This is necessary to enable women to make informed, autonomous decisions which represent the best possible alternative for them individually. Not only benefits and positive and negative side effects, but also the associated costs, the respective reimbursement situation, cost-effectiveness as well as ethical, social, and organisational aspects must always be transparently addressed.

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List of abbreviations

Abbreviation	Meaning
AMG	Arzneimittelgesetz (Medicinal Products Act)
GDPR	General Data Protection Regulation
GOÄ	Gebührenordnung für Ärzte (Fee Schedule for Physicians)
HIV	human immunodeficiency virus
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IUD	intrauterine device
LARC	long-acting reversible contraception
MDR	Medical Device Regulation
MPG	Medizinproduktegesetz (Medical Devices Act)
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ProdHaftG	Produkthaftungsgesetz (Product Liability Law)
RCT	Randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SHI	statutory health insurance

HTA overview

1 Background

1.1 Health policy background and commission

According to §139b (5) of Social Code Book V, Statutory Health Insurance (SGB V), statutory health insurance members, and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the ThemenCheck Medizin ("topic check medicine") website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts and a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance those deciding about health care services and structures. The HTA report will be made available to the professional community through the ThemenCheck Medizin website (www.iqwig.de). In addition, a lay summary of the results of the HTA report will be published under the title "HTA compact: The most important points clearly explained". This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

The choice of contraception depends on individual preferences and needs. The decisive factor may be safety, ease of use, or tolerability. Various hormonal and non-hormonal contraceptive methods are available to avoid pregnancy. The most commonly used contraceptive methods are condoms and oral contraceptive pills ("the pill") [5,6].

Another contraceptive method is the hormone-releasing intrauterine device (IUD). Hormonal IUDs consist of a T-shaped plastic device with a hormone reservoir as well as a retrieval cord. Following a general gynaecological examination, IUDs are inserted into the uterus by a gynaecologist. This is done transvaginally with the help of a speculum and an applicator. As a rule, no special pain therapy (analgesia) is necessary. The IUD consistently releases a small amount of hormone (levonorgestrel) in the uterus, and, from the moment of insertion, it prevents the implantation of a fertilised egg /blastocyst in the uterine lining [5].

Copper IUDs represent another option for non-hormonal contraception. Copper IUDs consist of a T-shaped or anchor-shaped plastic frame wrapped with a copper wire and feature a retrieval cord. These IUDs are likewise inserted into the uterus by a gynaecologist. Copper ions have a spermicidal effect. For up to 5 years, the copper IUD as a foreign body additionally reduces the ability of the fertilised egg or blastocyst to implant in the lining of the uterus [5].

Copper intrauterine balls and copper intrauterine chains employ a very similar principle of action and can be deemed advancements of copper IUDs [7]. Compared to spiral IUDs, copper intrauterine chains have no side arms and are fixed in the fundal myometrium (the upper muscle layer of the uterus opposite the cervix). Due to their more flexible shape, the latter can be used even in patients with a narrow uterine cavity, e.g. in young women or those who have already experienced IUD expulsion. Copper intrauterine balls are shaped like a copper bead chains which 3-dimensionally expand in 2 axes to form a sphere once they have been inserted into the uterine cavity (stent technology). This is intended to result in a tailored fit and prevent perforations [7].

The removal of both types of IUDs is likewise carried out by a gynaecologist rather than by users themselves. Both copper IUDs and hormonal IUDs are available in similar versions from different manufacturers.

Overall, how women experience and evaluate the various side effects of hormonal and copper IUDs varies from person to person.

1.3 Health services situation

According to a representative survey conducted by the Federal Centre for Health Education (Bundeszentrale für gesundheitliche Aufklärung, BZgA) in 2018, hormonal or copper IUDs are used for contraception by a total of 10% of sexually active women aged 18 to 49 in Germany [8,9]. In general, IUD use is more common among women aged 40 to 49 years (20%) than among women aged 18 to 29 years (5%) [9]. This makes the IUD the third most commonly used contraceptive. Oral contraceptives and condoms are the most widely used contraceptives in Germany, accounting for 47% and 46% respectively. Many couples use several contraceptive methods in parallel [8]. The BZgA survey reports an overall critical attitude, especially among younger people, towards hormonal contraceptive methods. At 48%, almost half of the respondents agreed with the statement that contraception with hormones has "negative effects on the body and mind" [9].

Publicly available sources report that hormonal IUDs cost between €300 and €400 for an effectiveness period of up to 6 years, while copper IUDs cost between €120 and €450 for an effectiveness period of up to 5 years [10]. This includes the consultation and insertion by the physician. The costs of annual ultrasound checks of IUD positioning, which amount to about €40, must be added to this amount.

In women up to the age of 22 years, the statutory health insurance (SHI) covers IUD costs, as it does for other contraceptives [10]. From the age of 18 years, a co-payment of 10% of the dispensing price, minimum €5 and maximum €10, is required [11].

1.4 Concerns of those proposing the topic

This HTA report is based on the suggestion by a member of the public who anticipates that both copper and hormonal IUDs are reliable means of contraception which differ in their positive and negative side effects. She is therefore particularly interested in the question of how the various positive and negative side effects of copper and hormonal IUDs are experienced and evaluated by women.

2 Research questions

The aims of this investigation are to

- assess the benefit of contraception with copper IUDs compared to hormonal IUDs in women of childbearing age with a desire or indication for contraception with regard to patient-relevant outcomes. The focus of the assessment is on whether the 2 types of IUDs differ in terms of their positive and negative side effects.
- determine the costs (intervention costs) and assess the cost-effectiveness of contraception with copper IUDs compared to hormonal IUDs
- review ethical, social, legal, and organizational aspects associated with the medical intervention.

3 Methods

This HTA report is prepared on the basis of General Methods 6.0 [12].

3.1 Stakeholder survey

In preparation for the other parts of the report and in parallel with the preparation of the HTA report protocol, patient-relevant aspects as well as relevant ethical, social, legal, and organisational aspects of both types of IUDs were discussed with IUD users.

The surveys of IUD users took the form of focus group and one-on-one interviews. These interviews were structured using an interview guideline. The interviews were recorded on audio files and subsequently written down and analysed for content.

3.2 Methods of the benefit assessment

Studies with women of childbearing age with a desire or indication for contraception were included in the HTA report. The intervention to be assessed is contraception with copper IUDs (non-hormonal copper-containing intrauterine devices, Cu-IUDs). Since copper intrauterine chains and copper intrauterine balls (frameless intrauterine devices) share the identical mechanism of action, these devices were to be investigated as well. The comparator intervention was contraception with hormonal IUDs (levonorgestrel-containing IUDs; LNG-IUDs).

The following patient-relevant outcomes are taken into account in the assessment:

- Effectiveness / unwanted pregnancy
- Side effects or adverse events, e.g.:
  - pain
  - amenorrhoea (absence of menstruation)
  - strength of menstruation
  - abdominal pregnancy
  - infections
  - risk of breast cancer, cervical cancer, endometrial cancer
  - (sub)fertility
  - improper placement
  - displacement/expulsion of the IUD
  - perforation (piercing) of the uterine wall

- Health-related quality of life
- Outcomes analysed for supplementary information:

The outcome “wearing time” is analysed for supplementary information because it may indirectly provide information on how women perceive positive and negative side effects. However, (greater) benefit cannot be derived based on this outcome alone.

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

A systematic literature search was conducted in the following databases, among others: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase, Cochrane Database of Systematic Reviews, and HTA Database.

The following sources of information and search techniques were additionally used: study registries and systematic reviews.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, outcome-specific and study-level criteria for risk of bias were assessed, and the risk of bias was rated as high or low in each case in accordance with the General Methods 6.0 [12]. The results of the individual studies were described, organized by outcomes.

In addition to comparing the results of the individual studies, metaanalyses and sensitivity analyses as well as the investigation of effect modifiers were to be conducted. A final summarizing evaluation of the information was carried out in any case.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available, or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

3.3 Methods of the health economic assessment

To calculate intervention costs, the average resources required directly when performing the experimental and comparator intervention were estimated. For this purpose, the services directly associated with the intervention as well as the experimental and comparator intervention were taken into account. The relevant regulated or negotiated prices of these

services were used wherever possible. Where an intervention took more than 1 year, the average annual cost per woman was reported. Reimbursable and non-reimbursable costs were listed separately.

The systematic overview of health economic studies included cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses in German or English.

As part of the focused information retrieval, a systematic literature search was conducted in the MEDLINE and Embase databases as well as the Health Technology Assessment Database. The following sources of information and search techniques were additionally used: systematic reviews.

The identified quotes were selected by one reviewer, with a second person doing quality assurance. Data extraction relied on standardized tables based on the criteria of the CHEERS statement [13] and the European Network for Health Technology Assessment (EUnet) HTA adaptation toolkit [14]for the assessment of reporting quality and transferability.

The cost-effectiveness results reported in the studies were juxtaposed against the authors' conclusions, particularly concerning study quality, transferability to the German healthcare system, and the use of outcomes deviating from the benefit assessment.

3.4 Methods regarding ethical aspects

For the analysis of ethical aspects, scoping searches were conducted in the following information sources:

- ETHMED
- MEDLINE
- data from regional registries, laws, regulations, or directives
- interest-dependent sources of information, e.g. websites of interest groups, health insurance funds
- manual search in Google / Google Scholar

Additionally, the following documents were checked for potential ethical arguments and aspects:

- studies included in the benefit assessment
- studies included in the health economic assessment
- the protocol for documenting the discussion with the surveyed women (IUD users)

To support the quality of the ethical analysis, the reflective-thoughts method, i.e. reflection informed by the authors' knowledge regarding potential social arguments and aspects, was applied as an additional source of information [15].

One reviewer screened the sources from all information sources employed for the scoping searches or all other documents for statements on ethical arguments and aspects of the technologies to be investigated.

The information on ethical aspects was analysed taking into account the overarching questions of Hofmann's simplified questionnaire [15], but was also oriented towards the framework for the ethical evaluation of public health measures according to Marckmann [16]. The framework according to Marckmann was extended for the scope of comparative consideration of 2 interventions.

3.5 Methods regarding social, legal, and organizational aspects

For the analysis of social, legal, and organizational aspects, scoping searches were conducted in the following information sources:

- MEDLINE
- Data from regional registries, laws, regulations, or directives
- interest-dependent sources of information, e.g. websites of interest groups, websites of health insurance funds, etc.
- manual search in Google / Google Scholar

Additionally, the following documents were checked for potential social, legal, and/or organizational arguments and aspects:

- studies included in the benefit assessment
- studies included in the health economic assessment
- the protocol for documenting the discussion with the surveyed women (IUD users)

One reviewer screened the information from all sources employed in the scoping searches or all other documents for statements on social, legal and/or organizational arguments and aspects of the technologies to be investigated.

4 Results: Stakeholder survey

A total of 10 women were interviewed using the structured interview guideline. Three focus groups with 2 to 3 women each and 2 one-on-one interviews were conducted. The selection of the women was targeted in particular with regard to age (so-called "purposive sampling") in order to include a broad range of women of the relevant age groups. The interview guideline covered the following areas:

- experience with an IUD in terms of patient-relevant outcomes which are to be covered in the benefit assessment
- experience or ideas regarding economic, social, legal, or organisational aspects (including experience with counselling by physicians)

Characteristics of the women interviewed:

Except for 1 respondent, all women had concrete experience with 1 or more IUDs. One participant was interested in a hormonal IUD but had not yet come to a final decision. All women were SHI insured, and their highest educational attainment was an entrance qualification for all types of universities (*Abitur*) or for a university of applied science (*Fachabitur*). The average age was 36 years. Participants included 6 women who were younger than 35 years and 4 women who were 35 years or older (age range: 23 to 53 years). Four participants contributed information on hormonal IUDs (1 of them without any experience of her own), and 6 participants contributed information on copper IUDs. Most of the participants had already had their IUD for at least 2 years.

Results of the interviews:

All of the women had the primary goal of contraception.

Other goals mentioned were:

- not having to think about contraception for the next few years
- safety and continuity for a longer period of time
- bridging the time until menopause without fear of pregnancy

For hormonal IUDs, they also cited the arguments "fewer hormones than the pill", "stabilization of menstrual rhythms/bleeding", and "twice the security – if the IUD slips, I'll still have the hormones".

For copper IUDs, the primary arguments cited were "getting away from hormones", "negative experiences with hormones/pills" and "wanting to be hormone-free for a longer period of time".

Experience with the respective method (IUD) with regard to patient-relevant outcomes:

Preventing pregnancy

No pregnancies were reported/diagnosed.

The copper IUD became dislodged and was later lost in 1 participant, and it became ingrown in another participant. In this context, the women reported worrying about lacking reliable contraception during this period and about having been at risk of pregnancy.

Complications or pain during the procedure (pain on insertion)

The insertion of IUDs (as well as their removal) was described as painful (brief, but stinging / "extreme"). About half of the women had the IUD inserted without anaesthesia, but even those who had them inserted under anaesthesia reported brief, very unpleasant pain. In 2 to 3 women, the pain was "not so bad" (in some cases under anaesthesia or other preparatory medication such as misoprostol or ibuprofen). One woman described it as not bad and only very brief, even without anaesthesia. Some women reported circulatory problems immediately after insertion. Abdominal pain on the first day or the first few days afterwards was also reported by some ("maybe my body wanted to reject it").

Complications (longer term) after insertion (e.g. expulsion of the IUD)

Only a few specific complications were reported.

Copper IUDs:

- 1 became dislodged or was lost (use of a menstrual cup was identified as a possible problem by the person concerned), 1 became embedded ("had to be surgically removed, very painful").

Side effects (bleeding-related, e.g. change of menstrual cycle)

Hormonal IUDs:

- The majority of women view the absence or reduction of menstrual bleeding as a favourable result.
- With regard to experiencing no more bleeding (amenorrhoea), 1 woman reported the following: you lose conscious awareness of your monthly rhythm or where you are in your cycle. It is no longer possible to explain mood swings and other complaints with the timing of your cycle, which leads to uncertainty.
- Two younger women were also concerned that they would not be able to get pregnant after removal of the IUD.

Copper IUDs:

- The majority of women reported bleeding being heavier (especially in the first year) but not heavy enough to be very distressing or annoying. In addition, women reported longer bleeding periods or increased bleeding between periods.

Side effects (not directly related to the IUD, e.g. headaches, depressive moods)

Hormonal IUDs:

- In oral contraceptive pills, hormones are perceived as a problem, causing mood swings, etc. Hormonal IUDs are hoped to be associated with fewer side effects.

Copper IUDs:

- The majority reported some marked improvements in their general health due to the elimination of hormone-related side effects of oral contraceptives (e.g. self-assessed depressive moods, weight gain).
- Discontinuation of hormones is perceived as a relief.
- One woman initially reported changes in her skin due to the cessation of hormones. However, the situation improved with time, and this woman also found the discontinuation of hormones positive overall.

Experience or ideas regarding economic, social, legal, or organisational aspects (including experience with counselling by physicians)

Costs/Effort

- Costs are initially high, but ultimately, this was not an obstacle for any of the respondents.
- For young women, however, the costs are sometimes a critical factor (possible workarounds: financial support by parents, IUD purchase/insertion abroad at lower cost).
- Overall, the IUD is "not a cost issue" but represents a relevant alternative to the oral contraceptive pill.
- Two women addressed the fact that, over time, the IUD is rather inexpensive compared to the oral contraceptive pill.
- Paying for follow-up visits out of pocket was fine for all women, as these visits are perceived as important. Some physicians did not even charge these costs at all.
- Worry about IUD expulsion- "then the costs were incurred in vain"

Perception of the IUD

- Several women notice a foreign body (slight pricking, unpleasant idea of a wire / anchoring mechanism), while others did not notice it at all or only directly after insertion
- A gynaecologist negatively commented on copper IUDs ("like a rusty wire in a tree")
- Several partners report that they feel the IUD during sexual intercourse.

Fears or worries

- Fear of removal and associated pain
- Hormonal IUDs: fear of long-term exposure to hormones
- Copper IUDs: Fear of the IUD slipping/moving or being expelled (and the associated risk of unintentional pregnancy), fear of IUD getting embedded (losing ability to have children), fear of copper deposits in the body (rather diffuse fear)
- Slipping/expulsion: One woman reported that she "preferred not to have sexual intercourse for a few weeks after insertion so as not to take any risks until it was clear that the IUD was securely in place".

Quality of life

- Carefree, "becomes a non-issue", peace of mind for the next few years, no more worrying about contraception – not having to be bothered at all.
- Security – "bought with the IUD"
- Being able to have carefree and unplanned sex, no longer having to talk with the partner about contraception, not having to rely on the man
- Significant improvement in quality of life without hormones "if I had known this when I was 15" – no more mood swings.
- Peace and continuity at last

In addition, some specific questions were discussed with the women:

- Were you told about or introduced to the 2 contraceptive options (copper/hormonal IUD) by your gynaecologist?
- Have you received information about the 2 options?
- Where else did you look for or receive information?

IUDs seem to be discussed only when asked directly or when there is a desire to prevent pregnancy without using an oral contraceptive pill. Physicians tend not to address this topic without cause (it is occasionally broached as an option for the transition to menopause).

Physicians seem to primarily focus on hormonal IUDs, while copper IUDs “exist in the shadows”, although women are apparently increasingly asking for them.

Some physicians spoke out slightly (in 2 cases even very specifically) against a copper IUD and steered the decision in the direction of a hormonal IUD. Others were more open to copper IUDs (2 women report very good counselling here).

Most of the women had informed themselves via the internet or had heard about IUDs from friends or family members. Some physicians also explained IUDs well when asked. One woman reported that her physician clearly advised her against copper IUDs. Experiences of friends or family members seem to play a big role in the choice of an IUD.

Summary and conclusion of the interviews:

The interviewed women who had or still have a copper IUD were all satisfied, even though they themselves or their friends had sometimes had bad experiences with it (dislodgement, embedding). Being hormone-free is seen as a particularly winning argument / increase in quality of life. Hormonal IUDs are likewise predominantly rated positively, although the women were consistently unsure how much (further) strain the hormones put on their bodies and what the long-term consequences might be. On the one hand, women experienced fears of insertion, dislodgement, embedding, removal and the potential associated pain. On the other hand, they viewed this as being "a solution for several years" and the associated safety from pregnancy and spontaneity during sex as increasing their quality of life. To be sure that their IUD fits correctly, follow-up checks every 6 to 12 months are important to most women.

Although the survey cannot claim to be representative or complete, it did provide evidence of women's perceptions and experiences regarding patient-relevant outcomes and other aspects examined in this report. The results of the stakeholder survey can support the interpretation of the results of the benefit assessment and highlight relevant aspects for the further parts of the report. They are particularly important in this report, as one concern of the person proposing this report topic was to find out "how the various positive and negative side effects of copper and hormonal IUDs are experienced and evaluated by women".

Limitations / strengths of the interviews:

- Limited insights due to small/non-representative sample.
- Although the survey was neither representative nor complete, the results allow us to conclude that an extended survey of women (up to saturation) might provide further valuable insights into the preferences and experiences of women from different backgrounds and age groups.
- With regard to the women’s assessment of outcomes (e.g. amenorrhoea being seen as positive by some but being more of a concern for others), the results of the interviews

suggest a cautious/non-evaluative interpretation of the conclusions on some patient-relevant outcomes (primarily the ones related to bleeding).

- Patients' statements on the advice received from their physicians suggest that a structured survey of gynaecologists would be very useful in order to find out why, as reported by the interviewees, they do not provide balanced information about all available contraceptive methods.

5 Results: Benefit assessment

5.1 Results of the comprehensive information retrieval

All search strategies, search periods, and hit counts of the comprehensive information search are documented in Appendix A10 of the full report.

The information search in the bibliographic databases revealed 8 relevant RCTs for the research question (Rowe 2016 [17], Rezk 2019 [18], Sivin 1994 [19], Laporte 2020 [20], Anderson 1994 [21], Todd 2020 [22], Kakaire 2015 [23], Ramazanzadeh 2012 [24]), with a total of 10,372 women included (see Sections A3.2 and A9.1.1 of the full report).

Five of these RCTs were conducted with healthy women aged 18 to 43 years and at least 1 previous pregnancy [17-21], 2 RCTs included women aged 18 to 49 years with human immunodeficiency virus (HIV) infection and at least 1 pregnancy [22,23], and 1 RCT included 20 to 35-year-old women with dysmenorrhoea and at least 1 previous pregnancy [24]. The 2 studies in women infected with HIV were included in the benefit assessment because, from a clinical point of view, the presence of an HIV infection should not influence the contraceptive effect or the side effects of IUDs. With regard to the evaluated outcomes, transferability is therefore assumed.

No systematic reviews were rated as being current and of high quality or included for the identification of primary studies.

The information retrieval in the study registries resulted in 8 RCTs relevant for the research question. Three of these entries were attributed to RCTs already included [24-26]. The status remains unclear for 5 other studies, each of which was to be completed over 12 months ago [27-31]. Publications of results are therefore to be expected in the coming years. However, due to the comparatively low numbers of participants in these studies (N = 50 to 232), a relevant change in the overall conclusion of the present report is unlikely.

The last search was conducted on 27 January 2022. The search strategies for bibliographic databases and trial registries are found in the appendix.

Table 1: Study pool of the benefit assessment

Study	**Available documents**		
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Other Documents**
Studies on all women without comorbidities			
Rowe 2016	Yes [17]	No	No
Rezk 2019	Yes [18,26]	Yes [30]	No
Sivin 1994	Yes [19,32]	No	No

Laporte 2020	Yes [20,25]	Yes [28]	No
Andersson 1994	Yes [21,33-35]	No	No
Women with HIV infection			
Todd 2020	Yes [22]	No	No
Kakaire 2015	Yes [23,36]	No	No
Women with dysmenorrhoea			
Ramazanzadeh 2012	Yes [24]	Yes [29]	No

5.2 Characteristics of the studies included in the assessment

5.2.1 Study design

All studies were conducted with women who had a history of at least 1 pregnancy (see Table 13 of the full report). The median age of the women was between 26.5 and 31.4 years (see Table 14 of the full report). The participants of 5 of the 8 included RCTs included had no concomitant diseases, those of 2 studies had HIV infection, and those of 1 study had dysmenorrhoea. The number of participants ranged from 140 to 3836 (median: 516.5). The 3 largest studies were conducted with healthy women and were multicentre, international studies. The 2 studies with women with HIV infection were conducted in South Africa and Uganda, while the remaining 3 studies were conducted in Egypt, Brazil, and Iran. Follow-up observation ranged from 3 months to 10 years, with the 3 largest studies also having the longest follow-up observation.

In 7 of the 8 included studies, the intervention treatment consisted of a copper IUD with 380 mm^2 surface area. In 1 of the studies [21], the surface area was 200 mm^2. The comparator treatment were hormonal IUDs with 52 mg levonorgestrel (20 µg/day). In the 2 studies which treated women with HIV infections, antiviral therapy was additionally administered. The remaining 6 studies did not report any concomitant medications.

5.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from all 8 studies. Table 2 shows the overview of these data. The outcomes can be pooled into the 6 outcome groups "pregnancy and discharge", "effects on menstruation", "pain", "inflammation and other complaints", "reasons for removal", and "health-related quality of life". Other outcomes were documented in the included studies but not deemed to be patient-relevant on the grounds of either not being predefined as outcomes or having been collected by means of non-validated questionnaires; these are reported as "supplementary outcomes" (acceptance, satisfaction, and sexual arousal). No benefit or harm was derived from these outcomes.

Both the reviewed qualitative research and the survey of those affected suggest that women perceive the accompanying and side effects of IUDs very differently. For example, some women perceive the decrease or absence of menstruation positively, while others experience it as frightening and unnatural. For this reason, we avoid the terms "benefit" and "harm" in the corresponding outcome groups and instead quantify the occurrence (less frequent / more frequent occurrence).

Table 2: Matrix of reported outcomes

Study	Outcome groups, patient-relevant outcomes																									Supplementary outcomes							
	Pregnancy and expulsion				Effects on menstruation						Pain			Inflammations and other complaints			Reasons for removal								HR-QoI								
	All	Intrauterine	Ectopic	IUD expulsion	All	Absence of menstruation (amenorrhoea)	Reduced menstruation (hypomenorrhoea)	Increased menstruation (hypermenorrhoea)	Irregular cycle	Vaginal discharge	All	Menstrual pain (dysmenorrhoea)	Pain during IUD insertion	Inflammation in the abdomen	Inflammatory or other diseases of the genital organs, urinary tract and breast	Other complaints, possibly hormonal	Removal for possibly hormonal reasons	Removal for IUD-related or other reasons	Removal for other, non-IUD reasons	Removal for inflammatory or other diseases of the genital organs, urinary tract and breast	Removal due to other complaints (possibly also hormonal)	Removal due to menstrual problems	Removal due to pain	Removal due to planned pregnancy or other personal reasons	Health-related quality of life	Request for removal of the IUD	Removal of the IUD before the end of the study	Recommendation of IUDs to others	Overall satisfaction and acceptance	IUD not acceptable	Sexual arousal	Planned pregnancies after removal	Measurable HI viral load
Rowe 2016	●	●	●	●	●	●	●	●			●			●			●	●	●														
Rezk 2019					●			●	●	●	●															●	●	●	●				
Sivin 1994	●		●	●	●	●		●	●		●	●	●		●	●					●	●	●	●									
Andersson 1994	●		●	●	●	●					●					●	●				●	●	●	●	●							●	
Laporte 2020				●																	●	●		●									
Ramazanzadeh 2021												●													●				●				
Todd 2020	●	●	●	●		●		●	●	●	●	●			●	●		●															●
Kakaire 2015	●			●		●		●		●	●					●		●		●		●	●	●		●	●	●	●	●	●		

5.4 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as high for all 8 studies. This was primarily due to study participants and treatment providers not being blinded. Further, it remained unclear in 5 of the 8 studies whether reporting was independent of knowledge of the results. In 2 studies, outcome-independent reporting was clearly not present. In 5 studies, further aspects were identified which indicated a high risk of bias across outcomes.

Since the risk of bias on the study level was already rated as high, the outcome-specific risks of bias were not assessed separately but rated as high.

5.5 Results on patient-relevant outcomes

In the present benefit assessment, conducting a quantitative synthesis of data results (metaanalysis) did not appear to be meaningful. For none of the included outcomes was the analysis and presentation of results from the 8 included studies sufficiently homogeneous. This was due to heterogeneous outcome operationalization (e.g. very different reasons for IUD removal), different lengths of follow-up observation (1–7 years), differently reported results (e.g. absolute numbers per 100 women versus numbers per 100 contraceptive years / person-years) and different analytical procedures underlying these results, which meant that reported percentages were in most cases impossible to match with absolute frequencies (e.g. results from different survival analyses, see Table 11 of the full report). In addition, most publications lacked information on the dispersion of the reported rates or the differences between these rates. Calculating event rates for a specific period (e.g. 1 year) did not appear meaningful because it was furthermore not possible to assume a uniform distribution of the occurrence of events over the observation periods for any of the outcomes (violation of proportional hazards assumption; see, e.g. Table 49 and Table 50 of the full report for some outcomes).

Due to the large number of existing outcomes, they are pooled in 7 outcome groups below. A detailed presentation of the available evidence for each outcome can be found in Table 2. The evidence was derived based on the results of the individual studies according to the specifications of the IQWiG General Methods [12]. In the case of moderate certainty of results, heterogeneous studies and the presence of 2 or more studies, it is possible to derive an indication only if homogeneous or clearly equidirectional effects were present (see Table 3). It was possible to derive a hint either in the presence of 1 study with a statistically significant effect or in the presence of 2 or more studies, a heterogeneous study situation, and the presence of moderately equidirectional effects (see Table 3).

5.5.1 Results for the outcome group “pregnancy and expulsion”

Of the 4 outcomes in this outcome group ("pregnancies/all", "pregnancy/intrauterine", "pregnancy/ectopic" and "expulsion of IUD"), only one ("pregnancies/all") showed evidence

of slightly less effective contraception with copper IUDs compared with hormonal IUDs (see Table 16, Table 17, Table 18, Table 19 of the full report).

Results on the outcome "pregnancies/all" were provided by 5 studies (Rowe 2016, Sivin 1994, Andersson 1994, Todd 2020, Kakaire 2015). Conducting a metaanalysis was not meaningful due to the heterogeneity of the studies, measurement times, and operationalizations. All studies consistently report more frequent pregnancies in the copper IUD group than in the hormonal IUD group. Two of the 5 included studies reported significant differences in favour of hormonal IUDs. According to IQWiG's methods [12], direction and effects are therefore moderately conclusive. Reviewing the evidence at the individual study level, a hint of a difference between the IUDs for the outcome "all pregnancies" can be derived (more frequent occurrence of pregnancies in the copper IUD group).

However, for the 3 other outcomes in this outcome group, "pregnancies (intrauterine)" (2 studies, non-conclusive; Table 17 of the full report), "pregnancy (ectopic)" (4 studies, non-conclusive; Table 18 of the full report) and "IUD expulsion" (6 studies, non-conclusive, divergent; Table 19 of the full report), it was not possible to derive any hints or indications.

5.5.2 Results for the outcome group “effects on menstruation”

This outcome group combined 6 outcomes ("effects on menstruation / all", "absence of menstruation (amenorrhoea)", "reduced menstruation (hypomenorrhoea)", "increased menstruation (hypermenorrhoea, menorrhagia)", "irregular cycle", and "vaginal discharge"). Conducting a metaanalysis was not meaningful due to the heterogeneity of the studies, measurement times, and operationalizations. The available evidence was therefore determined in a qualitative manner. For 3 of the 6 outcomes, it was possible to derive a hint of a difference between the IUD types.

For the outcome "absence of menstruation (amenorrhoea)", results were available from 5 studies (Rowe 2016, Sivin 1994, Anderson 1994, Todd 2020, Kakaire 2015; Table 21 of the full report). They were rated as "moderately conclusive". A hint of less frequent occurrence was derived for copper IUDs.

For the outcome "reduced menstruation (hypomenorrhoea)", results from 1 study with a significant outcome (Rowe 2016; Table 22 of the full report) were available. Therefore, a hint of less frequent occurrence with copper IUDs was derived.

For the outcome "increased menstruation (hypermenorrhoea, menorrhagia)", results were available from 5 studies (Rowe 2016, Rezk 2019, Sivin 1994, Todd 2020, Kakaire 2015; Table 23 of the full report). They were rated as "moderately conclusive". Therefore, a hint of more frequent occurrence with copper IUDs was derived.

However, it was impossible to derive any hints or indications for the 3 outcomes "effects on menstruation / all" (4 studies, divergent results; Table 20 of the full report), "irregular cycle" (3 studies, non-conclusive; Table 24 of the full report) and "vaginal discharge" (3 studies, non-conclusive, divergent; Table 25 of the full report).

5.5.3 Results for the outcome group "pain"

This outcome group combined 3 outcomes ("any pain", "menstrual pain (dysmenorrhoea)" and "pain on IUD insertion"; Table 26, Table 27, Table 28 of the full report). Due to the above-described heterogeneity of the analysis and presentation of results, it was impossible to conduct any metaanalyses for these outcomes as well.

There were no detectable differences between the IUDs were found for any of the 3 outcomes. No hint, indication, or proof of an advantage of one of the IUD types can be derived when analysing at the evidence at the individual study level: "any pain": 6 studies, non-conclusive, divergent; "period pain (dysmenorrhoea)": 3 studies, non-conclusive; "pain on insertion of IUD": 1 study, not significant.

5.5.4 Results for the outcome group "inflammation and other complaints”

This outcome group combines 3 outcomes ("inflammation in the abdominal cavity", "inflammatory or other diseases of the genital organs, urinary tract and breast", and "other complaints, possibly hormonal"). Due to the above-described heterogeneity of operationalizations, analyses, follow-up observation periods, and analyses of results, it was impossible to conduct any metaanalyses for these outcomes. For 1 of the outcomes, it was possible to derive a hint of a difference for the IUD types.

For the outcome "other complaints, possibly hormonal", which includes, e.g. acne, nausea, depression, and weight changes, results from 4 studies were available (Sivin 1994; Andersson 1994, Todd 2020, Kakaire 2015; Table 31 of the full report). They were rated as "moderately conclusive". A hint for a less frequent occurrence was derived for copper IUDs. However, this outcome’s subcategories of anaemia, weight gain, and acne, which occurred statistically significantly more often with the copper IUD, form an exception.

For the outcomes "inflammation in the abdomen" (1 study, not significant) and "inflammatory or other diseases of the genital organs, urinary tract and breast" (2 studies, not conclusive), there were no detectable differences between the IUD types (see Table 29, Table 30 of the full report). Thus, no hint, indication, or proof of an advantage of one of the IUD types can be derived.

5.5.5 Results for the outcome group "reasons for withdrawal”

In this outcome group, the results are combined into 8 outcomes ("possibly hormonal reasons", "IUD-related or other reasons", "other, non-IUD-related reasons", "inflammatory or other diseases of the reproductive organs, urinary tract and breast", "other complaints [possibly also hormonal]", "menstrual problems", "pain", and "planning a pregnancy or other personal reasons"). Due to the described heterogeneity of operationalizations, analyses, follow-up observation periods, and analysis of results, it was impossible to conduct any metaanalyses for these outcomes either. For 1 of the 8 reasons for removal, it was possible to derive a hint of less frequent occurrence with copper IUDs.

The outcome "other, non-IUD reasons" was measured in 1 study (Rowe 2016; Table 32 of the full report). Removals were statistically significantly less frequent with copper IUDs, so a hint was derived in this regard.

There were no demonstrable differences between IUDs for the other 7 outcomes (see Table 32, Table 33, Table 35, Table 36, Table 37, Table 38, Table 39 of the full report): "possibly hormonal reasons" (2 studies, non-conclusive) "IUD-related or other reasons" (3 studies, non-conclusive), "inflammatory or other diseases of the reproductive organs, urinary tract and breast" (3 studies, non-conclusive), "other complaints (possibly also hormonal)" (3 studies, non-conclusive), "menstrual problems" (4 studies, non-conclusive, divergent), "pain" (3 studies, non-conclusive, divergent) and "planned pregnancy or other personal reasons" (3 studies, non-conclusive, divergent). Thus, no hint, indication, or proof of an advantage of 1 of the IUD types can be derived.

5.5.6 Results for the outcome "health-related quality of life (HRQoL)"

This outcome was investigated in 1 study (Ramazanzadeh 2012). There was no detectable difference between the IUDs for any of the 8 subscales of the SF36 (see Table 40 of the full report). Thus, no hint, indication, or proof of an advantage or disadvantage of one of the IUDs can be derived.

5.5.7 Results for the outcome group "supplementary outcomes”

The "supplementary outcomes" were study outcomes which were either not predefined or collected using non-validated questionnaires. Therefore, no benefit or harm was derived from these outcomes.

In 3 of the 8 supplementary outcomes, copper IUDs showed more frequent occurrence: "request for removal", "removal before end of study", and "IUD unacceptable" (Table 41, Table 42, Table 45 of the full report). In 2 further outcomes, occurrence was less frequent in copper IUDs: "recommendation of the IUD to others", "satisfaction and acceptance" (Table 43, Table 44 of the full report). Two other supplementary outcomes exhibited no clear

differences: "sexual arousal" and "planned pregnancies after IUD removal" (Table 46, Table 47 of the full report). For the sake of completeness, the HI viral load from the 2 studies involving women with HIV infection was additionally reported as a "supplementary outcome"; no between-group differences were reported (see Table 48 of the full report).

Overall, the above-mentioned supplementary outcomes show that women tend to evaluate copper IUDs more negatively.

5.6 Overall evaluation of results

Evidence map

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes

Outcome	**Result (from the perspective of copper IUDs)**	**Conclusion on benefit**
Pregnancy and expulsion		
Pregnancies (all)	More common	⇘
Pregnancies (intrauterine)	No clear difference: contradictory study results	⇑⇓
Pregnancy (ectopic)	No difference	⇔
IUD expulsion	No clear difference: contradictory study results	⇑⇓
Effects on menstruation		
All	No clear difference: contradictory study results	⇑⇓*
Absence of menstruation (amenorrhoea)	Less common	⇗*
Reduced menstruation (hypomenorrhoea)	Less common	⇗*
Increased menstruation (hypermenorrhoea, menorrhagia)	More common	⇘
Irregular cycle	No clear difference: contradictory study results	⇑⇓
Vaginal discharge	No clear difference: contradictory study results	⇑⇓
Pain		
Any (subcategories back pain, abdominal pain, and headache)	No clear difference: contradictory study results	⇑⇓
Menstrual pain (dysmenorrhoea)	No difference	⇔
Pain during IUD insertion	No clear difference: contradictory study results	⇑⇓
Inflammations and other complaints		
Inflammation in the abdomen	No difference	⇔
Inflammatory or other diseases of the genital organs, urinary tract, and breast	No clear difference: contradictory study results	⇑⇓
Other complaints (possibly hormonal)	Less common (exceptions: anaemia/weight gain/acne)	⇗
Reasons for removal		
Possibly hormonal reasons	No clear difference: contradictory study results	⇑⇓
IUD-related or other reasons	No clear difference: contradictory study results	⇑⇓
Other, non-IUD reasons	Less common (7.54%)	⇗
Inflammatory or other diseases of the genital organs, urinary tract, and breast	No difference	⇑⇓
Other complaints (possibly hormonal)	No clear difference: contradictory study results	⇑⇓
Menstrual problems	No clear difference: contradictory study results	⇑⇓
Pain	No clear difference: contradictory study results	⇑⇓
Planned pregnancy or other personal reasons	No clear difference: contradictory study results	⇑⇓
Health-related quality of life (HRQoL)		
Health-related quality of life	No difference	⇔

⇗: Hint of (greater) benefit or hint of lesser harm
⇘: Hint of lesser benefit or hint of (greater) harm
⇔: No hint, indication, or proof; homogeneous result
⇑⇓: No hint, indication, or proof, heterogeneous result
* These outcomes are evaluated differently by women. Therefore, no benefit or harm can be attributed to a difference.

Table 4: Results for supplementary outcomes

Outcome	**Result (from the perspective of the copper spiral)**
Request for IUD removal	More common
IUD removal before the end of the study	More common
Recommendation of IUD to others	Less common
Satisfaction and acceptance	Less common
IUD not acceptable	More common
Sexual arousal	No clear difference
Planned pregnancies after removal of the IUD	No clear difference
Measurable HI viral load	No clear difference

Assessment of the volume of unpublished data

The search in study registers yielded 5 RCTs which have been completed more than 12 months ago and whose results have not yet been published. The status of these studies was therefore assessed as unclear. Three of the 5 studies were expected to be completed over 5 years ago; therefore, the results cannot be assumed to still be reported. Publication bias or the likelihood that the results of these studies would markedly alter the available evidence as presented in the current report appears rather low because all 5 studies enrolled a total of only 576 participants. The protocols also showed no evidence of any outcomes which were disregarded in the present report. Rather, subgroups which would be only of secondary importance for the present research question were investigated in some cases (IUD insertion immediately after termination or delivery). Only 1 of the studies investigated the Jadess hormonal IUD, which delivers 13.5 µg/day, a significantly lower dose than the studies included in the present report. Therefore, the results of the 8 RCTs presented here, with over 10,000 participants, can be deemed sufficiently robust.

Weighing of benefits versus harms

In summary, the differences between copper and hormonal IUDs are presumably rather minor. Both IUD types are effective contraceptives, and the expected harm in each case does not exceed this benefit. The hint in favour of the contraceptive effectiveness of hormonal IUDs appears to be rather minor in quantitative terms. As far as side effects are concerned, no clear advantages of either IUD were found. The reasons for removal were also almost equally distributed among both types of IUDs.

For many of the side effects and reasons for removal, their perception depends strongly on the women's individual preferences and situations in life. For example, the absence of menstruation may be perceived by some women as unpleasant and unsettling, while others may see it more as an advantage.

6 Results: Health economic assessment

6.1 Intervention costs

The intervention costs for the 2 types of IUDs are divided into the costs of the IUDs themselves (Table 51 of the full report) and the outpatient insertion costs, including 1 insertion, 1 removal, and several follow-up visits (see Table 52 to Table 57 of the full report). The average costs per year for the individual women are also shown in Table 58 of the full report.

SHI reimburses both types of IUDs for women under 22 years of age (see §24a SGB V on contraception as well as the Guideline of the Joint Federal Committee on contraception regulation and abortion [37]. Women aged 22 years and older must pay the costs of the IUD as well as insertion/removal out of pocket. All costs are shown separately in the tables in Section A4.1 of the full report for women under 22 years of age (SHI-reimbursed) and for those 22 years and older (self-payers).

While copper IUDs are deemed medical devices, hormonal IUDs are classified as medicinal products. The Lauer Taxe database [38] served as the source for the cost determination for both types of IUDs. The quantity structures are based on the Red List [39] or the product information provided by the manufacturers of copper IUDs as well as the SPCs for the copper IUDs and the information in the technical hormonal IUDs [40]. According to this information, the recommended duration of use of the various IUDs ranges from 3 to 6 years (see Table 51 of the full report); therefore, the cost of the IUD itself was assumed to be incurred only once in the respective period and the costs for follow-up checks multiple times.

If hormonal IUDs are prescribed at the expense of SHI, the manufacturer's and pharmacy discount documented in the Lauer Taxe apply to the pricing since they are medicinal products. As per the agreement between the National Association of SHI Funds and the German Pharmacists Association, the pharmacy dispensing discount has been fixed at €1.77 since 2015. The manufacturer's discount varies depending on the product (see Table 5).

As per §61 SGB V, women under the age of 22 years must pay a co-payment of 10% of the pharmacy retail price for both types of IUDs, with a defined minimum amount of €5 and a maximum of €10. IUD reimbursement by SHI can also be claimed by women who are to receive contraception with IUDs for medical reasons. This may be the case, for instance, if they are taking medications for which oral contraception is contraindicated. However, women – even those under 22 years of age – must always individually apply for their health insurance company to reimburse their IUD costs. After their 22nd birthday, women have to pay the full cost of the IUDs out of pocket.

To calculate the average cost of copper IUDs, a few products which are frequently used in Germany were selected as examples from the large number of products available (including

the copper chain and copper bead ball). They were selected in consultation with the clinical experts involved. In the case of hormonal IUDs, all products on the market were included. Although the Lauer Taxe does not list generics, various generic manufacturers offer the covered original products at the same prices, offering the same discounts.

Where IUD prescriptions were to be paid by SHI, the Uniform Value Scale (EBM) was used for the pricing of outpatient services which are necessary in the context of IUD insertion and follow-up visits [41]. The Fee Schedule for Physicians (GOÄ) with varying billing rates was used as a basis for the pricing of outpatient services for women 22 years and older [42]. In this case, the services are optional or represent individual health services (IGeL), which are to be paid out of pocket. The services which are billable via the Uniform Value Scale or the Fee Schedule for Physicians in the context of an IUD insertion were estimated with the help of the clinical experts. The selected IUD was presumed to be inserted and removed once within the recommended duration of use; the associated costs and those incurred during the usage period were assumed to be incurred only once. Further, the services actually billed vary depending on the practice, the woman, and the IUD; therefore, an outpatient cost range was formed. For self-payers, it is worth noting that the rates as per GOÄ may be billed at a single to 2.3 times of the fee rate. According to the clinical experts, billing at 3.5 times the fee rate is unrealistic and was therefore disregarded. The various GOÄ rates are also shown in the estimated ranges. Only the first ultrasound check-up after insertion is reimbursed by SHI for women who are 22 years or older [43]. Further ultrasound examinations to check IUD positioning, which gynaecologists recommend to be carried out every 6 to 12 months, must generally be paid for out of pocket. For calculation purposes, these costs were assumed to be incurred on average 4 times in 5 years.

As a result, a copper IUD or chain costs between €30 and €190, even at a recommended usage duration of 5 years. Hormonal IUDs, in contrast, cost between €130 and €210 for a duration of 3 to 6 years (Table 51 of the full report).

The outpatient costs for IUD insertion/removal in women under 22 years of age are between €80 and €130 based on Uniform Value Scale billing by SHI. For self-paying women aged 22 and over, these costs range between €100 and €300 based on Medical Fee Schedule billing (see Table 54 of the full report). Additional costs are incurred for the approximately annual follow-up examinations. Depending on whether the service is SHI-reimbursed or self-pay, it costs between €20 and €40 or between €20 and €50.

When IUD costs and outpatient costs are combined and broken down into annual costs per woman, the various assumptions, prices, and fees give rise to the picture presented in Table 5.

Table 5: Comparison of annual costs per woman incurred for copper and hormonal IUDs (in brackets: share of costs to be paid out of pocket)

Patient group	Women of childbearing age < 22 years (generally reimbursed by SHI)	Women of childbearing age ≥ 22 years (generally self-paying)
Copper-containing systems / IUDs	approx. €40–105 annually[a] (copay: approx. €15–35)	approx. €45–150 annually[a] (copay: approx. €40–140)
Hormone-containing systems / IUDs	approx. €60–120 annually[a] (copay: approx. €20–35)	approx. €60–170 annually[a] (copay: approx. €60–160)
IUD: intrauterine device a: The figures from Table 58 of the full report have been rounded to the nearest 5 or 10 for improved clarity.		

Concerning copper-containing systems, it must be noted that the costs of simple copper IUDs tend to be at the lower end, while newer systems (e.g. copper bead balls) tend to be at the higher end of the reported cost range. The specific advantages of newer systems over conventional copper IUDs, which might explain their higher costs, are also unclear. When comparing copper IUDs versus hormonal IUDs, it must also be noted that the ranges shown in Table 5 reflect the great heterogeneity in prices and outpatient costs of the respective IUDs under different billing conditions, for different women, and in different practice settings.

6.2 Systematic review of health economic evaluations

6.2.1 Results of the information retrieval

The various research steps identified a total of 2 relevant studies: Trussell 2009 [44] and Mavranezouli 2008 [45].

The last search was conducted on 20 January 2022. The search strategies for bibliographic databases are found in the appendix.

Table 6: Study pool of the health economic assessment

Study	Available documents [reference]
Trussell 2009	[44]
Mavranezouli 2008	[45]

6.2.2 Characteristics of the studies included in the assessment

The characteristics of the studies included in the assessment are summarised in Table 60 of the full report. Both studies represent cost-effectiveness modelling with a Markov model. The aim of the US study Trussell 2009 was to estimate the comparative cost-effectiveness of a total of 16 contraceptive methods (including copper and hormonal IUDs) as well as no

contraception from a health insurance perspective when modelled over 5 years. The study was funded with support from Bayer Healthcare Pharmaceuticals, USA. Analysing all included interventions, the study shows that, comparatively speaking, copper IUDs, male sterilisation, and hormonal IUDs are the most cost-effective contraceptive options in the United States. Sensitivity analyses show a strong influence of the costs of the respective contraceptive method, the costs of an unwanted pregnancy, and the modelling period in relation to the comparative cost-effectiveness of the alternatives.

The Mavranezouli 2008 study aimed to compare the cost-effectiveness of 4 long-term contraceptive methods (hormonal IUDs, copper IUDs, hormonal implants, and depot injections) from a National Health Service (NHS) perspective for England and Wales. In addition, the long-term methods were also compared with a short-term oral contraceptive method (birth control pill), a permanent one (female sterilisation), and no contraception. In this case, the modelling was conducted variably over 1 to 15 years to find out how the cost-effectiveness ratios change over time. In Mavranezouli 2008, the modelling was a preparatory part of the generation of a clinical guideline on long-acting contraception commissioned by the National Institute for Health and Care Excellence (NICE). As in Trussell 2009, the result across all interventions showed that all long-term contraceptive methods are less costly and more effective than oral contraception with the birth control pill and are therefore superior. The models which went beyond 5 years further showed that female sterilisation was the superior long-term contraceptive method over the longer period. The most cost-effective options in the model were copper IUDs and hormone implants (the latter are thin plastic rods about 3–4 cm in length which are placed under the skin in the upper arm and release hormones continuously for 3 years). Sensitivity analyses have shown that particularly the discontinuation rates for individual contraceptive methods markedly influence the relative cost-effectiveness of the long-term methods.

6.2.3 Results: health economic evaluation

The results of the included studies are presented in Table 64 of the full report. The calculated costs per woman and the incremental cost-benefit ratios are each provided in the currency and for the index year as presented in the study. To facilitate the comparison of the included study results, the cost data from Mavranezouli 2008 were inflation-adjusted to 2007 (that is, the index year of Trussell 2009). In addition, the cost data of both studies were converted into euros. For the conversion, the Consumer Price Index (CPI) [31] and the Exchange rate of the Organisation for Economic Co-operation and Development (OECD) were used, and the online conversion tool was applied (CCEMG - EPPI-Centre Cost Converter v.1.4 [ioe.ac.uk]; CCEMG - EPPI-Centre Cost Converter v.1.4 [ioe.ac.uk])

The results (Incremental Cost-Effectiveness Ratios, ICERs) of the 2 included models [44,45] with regard to the copper and hormonal IUDs on which this report focuses (Table 35 of the

full report) should be viewed in the context of all contraceptive methods modelled in each case. Trussell 2009 conclude, firstly, that compared to no contraception, any contraceptive method is superior in terms of cost-effectiveness. According to Trussell 2009, the most effective contraceptive methods are female/male sterilisation (98.8% to 100% effective), hormone implants (100% effective), and intrauterine contraceptive methods (copper IUDs: 99.6% effective; hormonal IUDs: 99.8% effective). In addition, IUDs are the most inexpensive contraceptive methods alongside male sterilization. In the overall picture, 5-year modelling shows that copper IUDs (as the least expensive alternative) is superior to all other contraceptive methods except hormonal IUDs, male/female sterilization, and implants. While the calculated ICER for male sterilisation and the ICER for hormonal IUDs are rated as low compared to copper IUDs, female sterilisation and implants each have an ICER that is over 3 times higher. The conclusion of the 5-year modelling identifies male sterilization as well as both IUD types as being the most cost-effective contraceptive methods.

In Mavranezouli, both types of IUDs and the implant are also found to be superior to oral contraceptives (i.e. more effective and less expensive). When comparing the IUDs to each other, copper IUDs are once again the most cost-effective contraceptive method. In the 5-year modelling, hormonal IUDs, unlike copper IUDs, are weakly dominated by implants, i.e. their ICER is higher than that of the implants'. In the overall picture, however, both IUD types, alongside implants, are deemed by the NHS to be cost-effective contraceptive methods, even if implants perform comparatively better than hormonal IUDs. It is emphasised that long-term contraceptive methods have better cost-effectiveness when used for a longer period and are therefore preferable from an NHS perspective, especially compared to oral contraceptives.

A comparison of the studies shows that the ICER of hormonal IUDs compared to copper IUDs was about 3 times higher in Trussell (USA) than in Mavranezouli (UK). This is due to the correspondingly higher incremental costs in the USA compared to the UK, caused in particular by the prices of hormonal IUDs and higher outpatient costs, at the same incremental effectiveness (2 additional prevented pregnancies per 1,000 women).

With hormonal IUDs being capable of preventing 2 more pregnancies per 1000 women annually (0.2%) compared to copper IUDs, the incremental benefit underpinning the calculations used in the models is within the range of the results of the present benefit assessment (compare Section 5.5.1). The cost data used in Trussell's US model [44], on the one hand, are intransparent and unsuitably prepared for comparison. Secondly, the US cost data are, per se, not transferable to the German context. The cost data from England [45], on the other hand, are transferable to a limited extent. In Mavranezouli, the annual costs per woman for hormonal or copper IUDs are approximately at the upper end of the range of intervention costs calculated (estimated) by us per woman and year and are therefore generally comparable. However, the cost estimates (price and quantity frameworks) are based

on very different sources and estimates, including very different aspects (e.g. Mavranezouli's control examinations over the entire wearing period are not included). They are therefore not directly comparable with our calculations of intervention costs.

Overall, however, hormone- and copper-releasing systems presumably exhibit good incremental cost-effectiveness in the German context as well, given their long service life, high effectiveness, and comparatively low costs. This is particularly true compared to oral contraceptives as well as compared to condom use, which are currently among the most widely used contraceptive methods in Germany according to a BZgA study [10].

7 Results: Ethical, social, legal, and organizational aspects

7.1 Results on ethical aspects

The investigation of ethical aspects of copper IUDs and hormonal IUDs initially showed that the 2 contraceptive types do not exhibit any relevant differences. They are very similar in terms of the expected benefits they both exhibit, especially pregnancy prevention. The use of both IUD types is also associated with potential harm and discomfort, which differ in nature but are also comparable in outcome. However, the potential damage does not exceed the expected benefit. The IUDs both have a demonstrated impact on autonomy. They also do not differ in ethical, justice-related repercussions, and both are comparatively cost-effective interventions from a health economic perspective. For the detailed evaluation, see Table 67 of the full report.

Although both IUD types are comparable from an ethical point of view, they show differences especially in their potential side effects. The study thus focused on the effects of these differences, especially with regard to autonomy in the sense of making a self-determined choice between copper and hormonal IUDs.

Specifically,

the approach to the ethical aspects of the question of contraception in the comparison of copper versus hormonal IUDs was guided by the medical ethical principles of beneficence, nonmaleficence, respect for autonomy, and justice [46,47]. Against this background, the two IUD types to be compared were contrasted and evaluated in terms of "expected benefits", "potential harms and burdens", "effects on autonomy", "ethical, justice-related repercussions" and "expected efficiency" [48,49].

The scoping search in the MEDLINE database produced 4 usable hits. In addition, 1 study included in the benefit assessment was usable for the analysis of ethical aspects. The studies included in the health economic assessment did not reveal any additional ethical arguments. The same applies to searches in the ETHMED database, scoping searches for relevant laws, ordinances, or guidelines, and searches for interest-dependent information sources.

The results from the benefit assessment were additionally used to inform the aspects "expected benefit" and "potential harm and burden", and the results from the health economic evaluation for expected efficiency. Finally, the syntheses from the interviews with IUD users were used.

The following description of the main results focuses on the ethical aspects "expected benefits", "potential harms and burdens", and "impact on autonomy".

Expected benefit: Overall, both copper IUDs and hormonal IUDs exhibit the expected benefit: both IUD types fulfil their purpose by preventing pregnancies. The difference in effectiveness as revealed in the benefit assessment was rated as minor. In addition, both the interviewed women (see Section 4) and the qualitative research [50] report that the long-term effect of these contraceptives has further advantages, e.g. the resulting independence from individual sexual and contraceptive behaviour, a sense of security thanks to reliable contraception as well as freedom from worry and ease of mind – advantages which last for a long period of time.

Potential harms and burdens: The studies included in the benefit assessment report a variety of harm outcomes. These range from unintentional IUD loss (expulsion) and injuries or inflammation to pain, problems with menstrual bleeding, mood swings as well as skin and hair problems, distress caused by a partner being bothered by the IUD string during sexual intercourse (see Table 3). In summary, the "harm landscape" is very heterogeneous, so that it is not possible to attest a higher or lower risk of harm to either of the IUD types.

The bottom line is that the use of both IUD types is associated with potential harms and burdens. For harms such as intrauterine or ectopic pregnancies, pain, and inflammation, the studies from the benefit assessment show no clear differences, neither in the frequency of occurrence nor in the frequency of associated premature IUD removal (Table 3 see also [51]). The interpretation of the results is further complicated by the high risk of bias of all included studies.

It is obvious, but nevertheless worth mentioning, that hormone-based potential harms and strains can be clearly attributed to 1 of the IUDs. Women who deem it important to avoid these side effects or who generally want to do without the exposure to hormones are better off with copper IUDs. In contrast to copper IUDs, hormonal IUDs are associated with hormone-related side effects as potential harms. This applies primarily to effects on bleeding. While heavier menstrual bleeding may initially occur with copper IUDs, lighter bleeding or complete absence of menstruation can be expected with hormonal IUDs (see Section 5.5.2). All 3 of these scenarios – amenorrhoea, hypomenorrhoea and hypermenorrhoea – fall under "potential harm and distress", but they can be viewed quite differently by women: Some women are worried if their menstruation stops and they can no longer identify their cycle as the cause of mood swings, for example. Others, in contrast, deem the absence of menstrual bleeding to be an advantage (see Section 4). Other potential harms can likewise be linked to IUDs in this way (e.g. "reasons for removal"; see Table 67 of the full report).

Effects on autonomy: Firstly, both types of IUDs allow long-term reproductive control. A woman who makes a decision intentionally, with an understanding of the necessary information, of her own free will, and without external interference – meeting the conditions for self-determined decisions serving the principle of autonomy as per Beauchamp and

Childress [52]– acts in a self-determined manner and thus autonomously. In this respect, contraception with copper and hormonal IUDs promotes (reproductive) autonomy.

Several aspects are likely to restrict reproductive autonomy. They apply to both types of IUDs.

- Relevant for self-determined decision-making is the aspect of "forgetting the inserted IUD" [53], which originates from qualitative research: While the aspect of "forgetting" has clear advantages, e.g. in comparison with oral contraceptives, which women must remember to take every day, it is also associated with a disadvantage. Forgetting eliminates the intentional decision to (continue) reproductive control. **Recommendation:** This concern might be compensated for, e.g. by asking about it during regular gynaecological check-ups.
- Another relevant aspect is "fear of pain when inserting/removing the IUD", which was raised in the qualitative research as well as in the survey of IUD users (see Section 4 and [51]). Where this fear delays IUD insertion/removal, patients are not exercising their free will to initiate or continue long-term contraception and experience limited reproductive control. **Recommendation:** It should be checked whether it is possible to ensure painless insertion/removal (e.g. under anaesthesia).
- It is equally problematic when cost concerns delay IUD insertion or removal or when external influences, e.g. corresponding medical advice, delay insertion or removal. **Recommendation:** Cost regulations should ensure that professional IUD insertion or removal is possible in all cases in order to preserve reproductive autonomy and avoid injuries due to IUD self-removal.

Under recourse to the results of the benefit assessment and the harm outcomes, specifically the hormone-dependent ones, a further aspect of the ethical analysis should be particularly emphasised:

- Understanding the necessary information as the basis for a self-determined decision-making: Arguments from qualitative research show that the contraceptive choice is a preference-sensitive decision [54]. This supports the findings from the benefit assessment and the survey of IUD users, which showed that the very same IUD effects, e.g. the absence of bleeding in hormonal IUDs, are experienced favourably by some women but unfavourably by others.
- Where preferences play an essential role in decision making, the information status on benefits, harms, and burdens is crucial [55]: The better informed the woman, the better she can match her preferences with the expected consequences and on this basis make a self-determined decision regarding whether she wants an IUD contraceptive and if so, which one.

The findings from the survey of IUD users as well as the comments of our clinical experts suggest that the information provided by gynaecologists does not always meet the prerequisites for self-determined decision-making (see Section 4). The requirements regarding an information basis which supports self-determination are not met (1) if there is a lack of information about long-term contraception options with copper or hormonal IUDs as opposed to, e.g. oral contraceptives, (2) if there is a lack of evidence-based information about both types of IUDs, or (3) if medically unfounded guidance is given in favour of one or the other IUD types. This can end up in a woman being surprised by the side effects of the chosen IUD, being dissatisfied with it, and deciding to have the IUD removed prematurely. As a consequence, women undergo 2 avoidable invasive and potentially painful procedures: IUD insertion and removal. In addition, out-of-pocket costs arise if the woman is older than 21 years. **Recommendation:** Providing comprehensive information and counselling about expected benefits as well as potential harms and burdens – separately from the patient information and consent procedure prior to the intervention – helps women make an informed and self-determined decision about which contraceptive matches their preferences. Last but not least, this helps to avoid post-insertion side effects which the woman did not expect and which – avoidably – lead to premature IUD removal. What is required for a self-determined decision on reproductive control is therefore correct (evidence-based) and comprehensibly prepared information on the types of IUDs. Such information could, for example, be offered as an evidence-based decision-making aid to which gynaecologists refer patients in preparation for the treatment consultation. The decision for or against copper or hormonal IUDs should be embedded in a medical consultation to support shared decision making – separately from the informed consent discussion which is already required before the procedure.

7.2 Results on social aspects

The scoping search and findings from the systematic searches do not yield any studies specifically devoted to the differences between the 2 methods examined here with regard to social aspects. Nevertheless, some aspects can be identified which – due to the 2 methods' differing characteristics – might impact satisfaction and quality of life and thus also selection and use or duration of use.

7.2.1 Access, affordability and user characteristics

Two identified papers from the United States describe programmes which aim to increase the use of long-acting reversible contraception (LARC) through information campaigns and financial support [56-58]. One of the 2 studies focuses its interventions on younger women of lower socioeconomic status [57]. Both studies show high usage rates and satisfaction levels with both types of IUD. Both studies are non-randomised comparative intervention studies and thus inferior to the RCTs included in this report. Furthermore, whether the respective study settings and results are transferable to Germany remains questionable. In Germany,

problems with high pregnancy and abortion rates among underage women from socially precarious backgrounds are much less severe. However, out-of-pocket costs for IUD use were mentioned as a financial obstacle in the interviews with affected women. Likewise, the information deficit which was to be alleviated in both studies through information campaigns is definitely present in Germany as well [9].

Since the majority of the costs for long-acting contraceptive methods are incurred at the time of insertion, it may therefore be more appealing for women of lower socioeconomic status to resort to ad hoc contraceptive methods such as condoms or oral contraceptives, whose costs are spread over time. For social reasons, it seems sensible to point out to women at an early stage that although the costs for IUDs are mainly incurred at the beginning, they also ensure contraception for 3 to 6 years thereafter and that IUDs thus represent a comparatively inexpensive, highly reliable contraceptive method.

For Germany, the survey of IUD users (see Section 4) suggests that costs do not generally present an obstacle to the decision to IUD use. Especially in younger or underage women, this may still be the case nonetheless. From a social justice point of view, SHI reimbursement of any contraceptives for those under 22 years of age is therefore an important basis for enabling younger women to freely choose between contraceptive options. No studies addressing the socioeconomic aspects of contraception in Germany or women's preferences on these aspects were found. However, the non-representative surveys of clinical experts and users in the project provide initial evidence that young women under 22 years of age in Germany are very rarely offered IUDs for contraceptive purposes.

7.2.2 Values, attitudes and preferences

A study conducted in 14 European countries investigates the characteristics and preferences of women who have decided in favour of LARCs. It shows that the vast majority of women are over 30 years old. Convenience is cited as the most important argument for using LARCs [59]. The study comes from the European health care context, but its data are already 16 years old.

The fact that teenagers tend to be underrepresented in IUD prescriptions and use also served as the starting point of a US study comparing the risks and side effects of different IUDs on the basis of insurance data from over 90 000 women [60]. The authors suspect that American physicians have reservations about the use of IUDs in teenagers and that this could lead to their significantly less frequent use. Using a routine data analysis, the authors show that there are no marked differences between younger women (20-24 years of age) and older women (25–44 years of age) in terms of either complication or discontinuation rates [60]. In this regard, the question of transferability arises once again. The scoping search did not find any comparable studies from Germany or Europe. However, the BZgA survey also shows that IUDs are used fairly infrequently in Germany [10].

In the mentioned 2019 BZgA survey, women between 18 and 29 years of age in particular viewed hormonal contraceptive methods rather critically [61]. A total of 48% of respondents agreed with the statement that hormone-based contraception has "negative implications for body and soul". Only 33% thought that the birth control pill was suitable even for very young girls, and 55% rejected the statement that it was safe to use the birth control pill for years. In the non-representative survey of IUD users conducted prior to this report, a desire for hormone-free contraception was also expressed in particular by women under 35 years. In addition, our survey confirms a sceptical attitude towards hormones, particularly among younger women.

The studies found on this topic range share the finding that misconceptions, reservations, and information deficits on the part of users and professionals might reduce the use of these effective contraceptive methods. For example, a survey of more than 2,000 physicians in the United States shows that 16% to 18% of respondents had misconceptions and information deficits regarding the use of IUDs in obese women. Another interesting finding is that the rate of misconceptions is lower in institutions where IUDs are offered [62].

Cultural and religious conditions are another relevant factor influencing IUD use. One identified paper, for instance, highlights the problem that, for religious reasons, Catholic health facilities in the US rarely if ever offer IUDs or information about them [63]. For example, 97% of the websites of non-religious institutions in the United States contain information on these methods, compared to only 4% of those of Catholic institutions. Again, no comparable data from Germany were found. This example stands, pars pro toto, for various cultural and religious factors which may have positive or negative normative influences on contraception and the methods used. However, these influences seem to be less relevant in the choice between hormonal and copper IUDs.

Two identified reviews address women's wishes, attitudes, and preferences regarding LARCs. One of the papers includes 30 qualitative studies and identifies 5 key issues which are relevant to users [64]:

- influence of the respective method on bleeding (e.g. heavier menstruation)
- influence on the body (e.g. weight gain)
- method-specific characteristics (e.g. method of insertion)
- general characteristics (e.g. effectiveness, side effects)
- beliefs and misconceptions

The most important positive characteristic is described as "fit and forget", referring to the fact that after device insertion, users have peace of mind from the topic of contraception. Long-term action and effectiveness are other positively perceived characteristics. Irregular

menstrual bleeding, pain during insertion and removal, weight gain, and a foreign body sensation are mentioned as negative. As a limitation of this study, it must be noted that the searches were carried out in 2015, rendering the data of the included studies even older. Nevertheless, many of these arguments still seem valid 10 years after they were recorded.

The publication by Morison and Eagar is another systematic review of 54 qualitative studies (scoping review) but focusing on reproductive justice [65]. It concludes that the existing studies have 3 limitations:

- instrumentalist and individualist focus
- disregard of diverse perspectives (e.g. contraception in non-binary persons)
- noncritical focus on young women

For future studies in this field, the authors call for a better theoretical foundation as well as a broadening of the perspective beyond "dominant groups" (sexual and gender minorities) and to social and cultural factors.

7.2.3 Information, shared decision making

Physicians' reservations against copper IUDs were also mentioned in qualitative studies [62] and in the interviews with affected women conducted in the context of this report. Some of the interviewed IUD users reported that their physicians were critical of copper IUDs and did not really want to consult patients on this topic. These reservations could be in part based on the fact that the evidence comparing copper IUDs versus other contraceptive methods has not yet been systematically and clearly analysed. However, a prerequisite for the use of IUDs is that these options are presented to patients during the consultation.

Mann et al. [66] make a similar argument. The publication examines information campaigns in the United States on the use of LARCs, with a focus on the visual messages conveyed in over 100 cases. It concludes that in most campaigns, LARCs were presented as the best and supposedly only solution, leaving viewers with virtually no choice. The authors advocate for providing balanced information and financial support with informed user choice. Gomez et al. present a similar argument [67]. They discuss the US campaigns as the biased pushing of a specific option. Instead, they call for providing balanced information, a free choice of contraceptive method, and financial support which enables shared decision making of health professionals and users. The guidelines issued by the NICE in the United Kingdom likewise call for "woman-centred contraception". An informed decision should be made taking into account each woman's situation in life as well as her values and preferences [68].

Other studies found in the scoping search describe the quality of the required information [69,70], the development and evaluation of concrete information in the form of websites [71], interactive decision-making tools [72], or specific information on IUD use after abortions [73].

In summary, social and cultural factors play an important role in this health topic as well and should be taken into account in any planned information media or information campaigns. The provided information is not directed solely at users but also meant to inform physicians and healthcare staff in order to avoid misconceptions and reduce bias. To the best of our knowledge, this report is the first systematic review to date which brings together existing RCTs on this question. Hence, it will also contribute to improving the information available to professionals. Information for users and health professionals should be comprehensive, current, and balanced to enable informed decision-making and thus woman-centred contraception.

7.3 Results on legal aspects

Definitions and prerequisites

Legal aspects must be examined regarding the question of whether women should have hormonal IUDs or copper IUDs inserted to meet their contraceptive needs.

According to the protocol, the intervention to be investigated is the insertion of copper IUDs versus the insertion of hormonal IUDs in terms of side effects. Both types of interventions share the primary goal of contraception. The benefit assessment has shown that the goal of contraception can be achieved more or less equally well with both types of IUDs and that some of their side effects differ. The gynaecological intervention is the same for both IUD types, with both being inserted into the uterus by qualified healthcare providers.

7.3.1 Patient autonomy I – effective conclusion of contract

From a civil law perspective, patient autonomy finds its expression in the conclusion of a treatment contract, governed in the Federal Republic of Germany by the so-called Patients' Rights Act in §§630a ff BGB [74]. With these legal standards, the German legislator has laid down the rights and obligations of the parties in the context of treatment. Before the insertion of an IUD – regardless of which type – a treatment contract under civil law is concluded between the gynaecologist and the woman, with the consequence of the provisions of the Patients' Rights Act taking effect. An effective treatment contract presupposes the woman’s legal capacity as well as her capacity for consent [74].

This treatment contract for contraception does not differ for the 2 types of IUDs. According to established case law, this treatment contract on a contraceptive measure represents a contract with protective effect for third parties, meaning that third parties close to the patient (e.g. her husband or partner) are likewise covered by its protective effect [75]. Under some

circumstances, it offers the protected third party its own claims against the treating physician(s) in case of breaches of contractual obligations. In this ruling, a pregnancy caused by the faulty implantation of a subdermal contraceptive implant is declared as "damages" to be compensated not only to the pregnant woman, but also to the man liable for paying child support [76].

For a contract to be valid, the woman must have legal capacity, regardless of which IUD she has chosen. Legal capacity is the ability to independently carry out legally binding transactions. As a rule, this is unproblematic in the case of adult women with legal capacity who are themselves contracting parties. In some women under the age of 16, the consent of the authorised representative may be required.

For young people with private health insurance, only the primary insured person can apply for cost coverage and conclude the treatment contract (§192 VVG, §192 Rz 128; [77]. This is typically the young woman's father or mother.

7.3.2 Patient autonomy II – informed consent

As per §630d (1) sentence 1 German Civil Code (BGB; [74]) and §8 Model Professional Code for Physicians [78], before carrying out a medical measure, particularly an intervention in the human body or on health, the treatment provider is obliged to obtain the patient's consent. Interventions conducted without prior consent may constitute unlawful bodily harm under §223 or §229 StGB (§6 Rz.2,25ff [75]).

The decisive issue is the right of self-determination of each woman, who should be able to decide on treatment implementation as an autonomous subject. This in turn presupposes that the woman has been properly informed beforehand in an understandable manner and has been asked explicitly and unambiguously whether she consents to the measure (§630 d BGB, marginal no. 2 [74])). In the case of women under the age of 16, established case law states that their capacity to decide whether to insert any of the IUDs is determined by their mental and moral maturity.

According to §630e (1) German Civil Code (BGB) and established case law, it is the duty of the treating gynaecologist to inform the woman about the treatment options available in her case – use of a hormonal IUD versus a copper IUD – including their respective risks, prospects of success and, in particular, side effects. As the subject of the treatment, she is to be given the choice between the equally medically indicated treatment options [79]. Obtaining informed consent is primarily the duty of gynaecologists [80]. After duly informing the woman about the procedure, the goal is to obtain the woman’s informed consent as an expression of the right to self-determination (§6 marginal no. 1 ff [75]). Depending on who is a partner in the treatment contract under the German Civil Code, the informed consent of the respective relative capable of giving consent, the minor, or the legal representative must be obtained.

Since the insertion process is the same for both IUD types, the gynaecologist must inform the woman primarily about the IUDs' different (side) effects. In addition, the gynaecologist is obliged to provide financial information with regard to the expected costs of both IUD types.

IUD insertion can be associated with pain. According to a decision by the Dresden Higher Regional Court dated 7 August 2020 [81], however, legally effective consent to IUD insertion does not require the physician to inform about associated pain which is felt only for a short period of time (...). The same is likely to apply to hormonal IUDs unless and until a law or a supreme court ruling decides otherwise.

7.3.3 Patient autonomy III – data protection, confidentiality

Regarding both copper IUDs and hormonal IUDs, treating physicians are subject to the same data protection regulations, which are explained below, in the context of their contraceptive use. As part of medical treatment, information about the patient is collected and stored. Such health data are to be classified as "sensitive data" (Art. 9 General Data Protection Regulation [GDPR] [82] [83])) and thus constitute a special category of personal data. They are particularly worthy of protection. Health data are deemed to be personal data relating to the physical or mental health of a natural person, including the provision of health services, and revealing information about their state of health (Article 4 (15) GDPR). These data may be processed only for the listed purposes or within the framework of the stated justifications, e.g. for the defence of legal claims (Article 9 (2) (f) GDPR). In addition to the woman's explicit consent, which can be revoked at any time, Article 9 (2) GDPR provides that processing is permissible, e.g. if purposes of preventive health care, medical diagnostics, care or treatment in the health or social sector on the basis of a statutory regulation or on the basis of a contract with a health professional make this necessary (Article 9(2) lit h [83]).

Treating gynaecologists are subject to the same confidentiality regulations within the scope of their medical services, regardless of whether they insert a hormonal or copper IUD. The comprehensive medical duty of confidentiality results from §203 StGB [84] and the duty of confidentiality from $ 9 of the Model Medical Profession Ordinance (MBO-Ä [78]).

7.3.4 Market authorization – licensing / professional practice

Hormonal IUDs and copper IUDs legally differ in that these contraceptives are classified as either medicinal products or medical devices, with different resulting regulatory approval processes.

Although this method of regulatory approval does not directly influence the intervention in women, it is the only characteristic where the 2 types of IUDs are treated differently from a legal perspective. For women, this legal distinction has no effect on (1) the conclusion of the treatment contract or (2) the question of patient autonomy or (3) on the right to informational

self-determination. However, the gynaecologist inserting the IUD is obliged to provide information on the different modes of action of the IUD types, which form the basis for the differing classification of IUDs as either medicinal products or medical devices. By definition, medicinal products and medical devices are distinguished on the basis of their main intended effect, which is to be assessed objectively and scientifically (§3 No. 1 Medical Devices Act [MPG]) [85,86].

7.3.4.1 Copper IUDs

For all devices within the scope of Regulation (EU) 2017/745, the Medical Devices Act was replaced by the Medical Devices Implementation Act on 26 May 2021 [74,87].

The EU Medical Device Regulation (MDR) dated 5 May 2017 [88] now sets new legal standards because, in order to avoid fragmentation of the EU internal market, it has direct legal effect vis-à-vis those subject to the law, the "economic operators", without having to be transposed into national law [86]. The MDR establishes the legal requirements for the initial placing on the market (first making available by the manufacturer to trade or end users) and the first putting into service of medical devices (making available for use) in the European Economic Area. Article 2 No. 1 MDR legally defines a medical device [85].

A medical device is an instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability;
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood, and tissue donations and
- which does not achieve its principal intended action by pharmacological, immunological or metabolic means (Article 2 No. 1 MDR) [85].

Therefore, copper IUDs are by definition medical devices.

Copper IUDs are class III medical devices as per §4 MPG (13) [89]. The IUD material (copper) hinders fertilization and the implantation of a fertilised egg/blastocyst, an effect which lasts for up to 6 years.

As medical devices, copper IUDs are subject to the MP-VO liability regime and the regulations associated with it, i.e. in case of damage, the German Act on Liability for Defective Products and producer liability [85]. They define the responsible bodies for the approval and monitoring of copper IUDs.

In the case of medical damage (if due to a defective IUD, e.g. a broken one), this classification as a medicinal product versus a medical device leads to different bases for claims by women for damages against the manufacturers of the 2 types of IUDs (84 ff AMG [Medicinal Products Act], Act on Liability for Defective Products or producer liability [§823 BGB]) [85].

Damage from a medical device can have various causes. Not every problem with a medical device is due to a breach of duty by the manufacturer. For instance, if a woman has an allergic reaction to an IUD or if the physician makes a mistake when using it, the manufacturer is not liable. Only if the medical device itself has a defect and thus harms the life, body or health of the woman does liability lie primarily with the manufacturer (§1 Product Liability Law [ProdHaftG]). In this case, the woman must prove the product defect. The central element of strict product liability is §3 ProdHaftG, which lists the medical device's defects which give rise to compensation. Further prerequisites for the manufacturer's liability are the existence of damage to health and causality between the defect and the damage.

7.3.4.2 Hormonal IUDs

In practice, it is difficult to clearly differentiate medical devices from medicinal products. The decisive criterion is the product's main intended action. Medical devices shall not achieve their principal intended action by pharmacological, immunological, or metabolic means. The terms pharmacological, immunological, and metabolic action are explained in MEDDEV Guideline 2.1/3 and define medicinal products [86,90]. In hormonal IUDs, the contraceptive effect is particularly achieved by the continuous release of levonorgestrel. This is a metabolic action, which is defined as modifying the chemical processes involved in normal processes occurring in the human body, including starting them, stopping them, or changing their rate.

In the case of combination products consisting of a medical device and a medicinal product which form an integral whole, the principal legal basis depends on the main mode of action. [85].

Hence, hormonal IUDs are by definition medicinal products (§2 AMG [91]). They consistently release a small amount of the hormone levonorgestrel and protect against implantation of a fertilised egg/blastocyst for 3 to 5 years from the moment of insertion (depending on the type and amount released).

As medicinal products, hormonal IUDs are subject to the liability regime of the AMG and related regulations. In the event of damage, §§84 ff AMG therefore have priority. The AMG

defines responsible bodies for approval and monitoring. It defines responsible bodies for approval and monitoring.

§§84 ff AMG standardise liability for damage done by medicinal products and list the basic conditions under which the manufacturer of a medicinal product bears absolute liability for damage caused by medicinal products regardless of fault. Although the injured woman must prove that the – defective – hormonal IUD is the cause or at least a contributory cause of her health injury, she benefits from the presumption of causality as set forth in §84 (2) sentence 1 AMG [85,92].

A number of European directives have largely harmonised pharmaceutical law in the European Union in recent decades. As a directive of the European Parliament and of the Council, Directive 2001/83/EC acts indirectly by obliging the Member States of the European Union to transpose the directive into national laws. The scope of the directive was extended to the whole EEA in 2002. In Germany, these directives have been implemented by the Medicines Act and substatutory ordinances and administrative regulations and national [92].

7.3.4.3 Licence of the inserting physician

Inserting either type of IUD is deemed to fall under the practice of medicine and must be performed by a physician because medicine may not be practised by just anyone (§2 [1] German Medical Practitioners' Act). Training and state examination are standardized, and the German Federal Medical Regulation §4 (1) leaves further regulations (e.g. the State Board Examination Ordinance for Medical Licensure) to the legislature. Practising medicine requires state approval by a licensing authority, which is governed by the law of the respective federal state.

If SHI-insured women are to receive outpatient treatment in that they are to have any of the IUD types inserted, the physician must be a panel gynaecologist licensed for the treatment of SHI-insured women. The prerequisites for licensing are regulated by the German Social Code Book V, Regulations for Physician Licensure, and the Joint Federal Committee’s Demand Planning Guideline. The prerequisites cited in §28 (1) SGB V must be met to allow reimbursement of the medical service [93,94]. The professional group of gynaecologists is subject to so-called demand planning (§§99 ff SGB V), which means that there must be a need for care in order to be admitted as a panel gynaecologist (§95 (1) and (13) SGB V) [95].

7.3.5 Clinical application studies and intellectual property

No clinical studies were commissioned in the context of this HTA report, nor were they needed for its preparation; therefore, there was no need to examine the associated legal aspects.

IUD technology (of both hormonal and copper IUDs) has been invented a long time ago and should already be protected as the inventor’s intellectual property. For the purposes of this

HTA report, the question of intellectual property rights to the technology of the respective IUDs is not relevant for women.

7.3.6 Reimbursement of costs in the healthcare system

SHI-insured women up to the age of 22 are entitled to being provided with prescription contraceptives, i.e. to SHI covering their treatment costs as well as material costs (§24a para. 2 SGB V [96]). §24 a SGB V is put into concrete terms by the Federal Joint Committee's "Guideline on the Regulation of Conception and Abortion" [97].

Irrespective of IUD type, SHI covers costs only for women who have not yet reached the age of 22 (see Section 6). This reasonable rule raises the question of how to internally justify the exclusion of persons who are older than 22 but financially needy from the provision of contraceptives. This applies in particular to recipients of basic security benefits under SGB II and SGB XII. So far, case law has taken the view that the costs for the "pill", like for condoms, are to be paid out of the standard benefit, i.e. they do not have to be treated as one-off benefits to be covered by the basic security benefit institution [86].

All other women for whom contraception is not medically indicated, i.e. outside of a health treatment as per the guideline, are entitled only to the assumption of the costs of counselling and prescriptions (§24 a (1) SGB V [96]). This comprises the medical counselling, including the examinations listed in the above-mentioned guideline and the prescription of contraceptives.

In individual cases, contraception may need to be distinguished from medical treatment (e.g. in the case of genetically increased risk of health damage by pregnancy) in order to justify the reimbursability for women [98: 8]. Wenner points out that the exclusion of para. 2 applies irrespective of the intention to prevent pregnancy [86].

Outside SHI system, the assumption of costs depends on the respective private health insurance, the private health insurer's general insurance conditions, and the individually concluded insurance contract [77]; the model general insurance conditions of private insurers [99] do not provide for an obligation to reimburse. The individual contractual provisions are determinative.

With respect to costs, the GOÄ serves as Germany's mandatory pricing regulation. Privately insured women must pay for the respective IUD.

Further, the service, i.e. IUD insertion for contraceptive purposes – unless deemed to be medical treatment – is not a tax-free service and is therefore additionally subject to VAT [100].

7.4 Results on organizational aspects

The scoping searches did not reveal any evidence of organisational aspects which would particularly suggest differences between the 2 IUD types. Social and organisational aspects overlap to some degree. For example, the qualifications and opinions/attitudes of medical staff play a role when it comes to inserting IUDs. Reservations can lead to markedly reduced use [60,62,63].

This raises the question of how information and decision support reach affected women and at what point in the treatment pathway this information is needed and helpful [70-72]. NICE gives precise guidance on what information should be covered in the consultation [68]:

- effectiveness of contraceptives
- effective period
- risks and possible positive and negative side effects
- other advantages beyond the goal of contraception
- descriptions of insertion and removal
- when to seek professional help during the period of use

8 Discussion

8.1 HTA report compared with other publications

During the searches for this report, 16 systematic reviews or HTA reports were identified which were identified during the title and abstract screening (see Section A9.1.2 of the full report) as potentially relevant to the present research question. However, in the course of the full-text screening, it turned out that these publications' research questions did not correspond to the present one, so that none of the publications were usable. Most of these studies did not investigate the direct comparison between hormonal and copper IUDs. Some of them compared intrauterine contraceptive methods versus other forms of reversible long-term contraception (e.g. oral contraceptives or subdermal depot implants). No results were extracted from these publications for a direct comparison. Other reviews investigated the timing of insertion (e.g. immediately after birth or after abortion), IUDs with different dosages or surface sizes, or the usefulness of IUDs for emergency contraception. To the best of our knowledge, this is the first systematic review conducting a direct comparison between copper and hormonal IUDs. This seems remarkable because within the framework of the present HTA report, 8 RCTs were identified on this research question. The present report therefore provides new findings, particularly with regard to the positive and negative side effects of the 2 types of IUDs in comparison with each other.

Comparing the present results with the results of a 2019 conference of the Working Group on Women's Health appears to be of interest. The 2 presentations on hormonal IUDs (Buhse 2019 [101]) and copper IUDs (Florack 2019 [102]), which were based on a systematic review of the literature on the 2 types of IUDs, were of particular importance. Although no direct comparison was conducted, the focus was on women under 18 years of age, who could not be examined in this report.

The publication on hormonal IUDs arrives at similar results as the present HTA report with regard to the outcomes of contraception, pain during insertion, expulsion, and inflammation.

Florack 2019 [102] expands the horizon of the present report in that it includes non-randomised studies and reviews of such studies regarding positive and negative side effects of IUDs. One such review is Jatlaoui 2017 [103]. It compares safety, expulsion rates, inflammation, and other side effects in younger (≤ 25 years) versus older (> 25 years) women. Overall, the differences between age groups in terms of positive and negative side effects are rather minor. Jatlaoui (2017) describes a higher risk of IUD expulsion only for younger women compared to older women. The results of the review largely correspond to the results of the present benefit assessment, although the latter was not age-stratified and therefore allows no conclusions about differences between age groups.

8.2 HTA report compared with guidelines

Two guidelines were found which may be suitable for a comparison with the present HTA report. The German S3 guideline on hormonal contraception [104] and the UK guideline issued by the National Institute for Health and Care Excellence (NICE) [105].

The German S3 guideline primarily discusses hormonal IUDs. Copper IUDs are mentioned in 1 recommendation (evidence-based recommendation 4.E32): they are highlighted as the most effective option for emergency contraception and are particularly recommended for women with a BMI ≥ 30 kg/m^2 (evidence level 1-; recommendation grade B). However, emergency contraception is not the subject of this report, which is based on the suggestion by a member of the public. The guideline recommends hormonal IUDs for women with hypermenorrhoea, with the aim of reducing the intensity and duration of menstrual bleeding. This HTA report confirms the bleeding-reducing effect of hormonal IUDs (see results on amenorrhoea and severity of menstrual bleeding).

The English NICE guideline discusses various long-acting reversible contraceptive methods (including both IUD types, injections, and hormone implants), emphasizing their long-lasting contraceptive effect. The NICE guideline argues that these methods' long-term contraceptive effectiveness is of major benefit in preventing unwanted pregnancies when compared to user-action dependent methods such as oral contraceptives or condoms. The benefit assessment of this HTA report confirms the high and long-lasting contraceptive effectiveness of both types of IUDs, with slight advantages found for hormonal IUDs. The most important first recommendation in the NICE guideline is that women who need contraception should be informed about all available methods of contraception, including long-term methods, not least to ensure patient autonomy. The NICE guideline also emphasises that women's use and acceptance of IUDs requires for them to know their advantages and disadvantages, including efficacy (even non-contraceptive effectiveness), duration of action, risks / side effects, and the insertion and removal process as well as education about what to do in case of problems. Women should be properly and comprehensively informed, particularly about side effects and risks of IUDs, as well as made aware of non-contraceptive effects (e.g. bleeding-reducing effects of hormonal IUDs [up to and including amenorrhoea] and bleeding-increasing effects of copper IUDs). In this context, the NICE guideline emphasises the importance of well-informed and educated physicians who should be well trained in (1) the provision of adequate information to women about the advantages and disadvantages of IUDs and (2) the insertion and removal of IUDs and the recognition and treatment of any complications and side effects which may arise in connection with IUDs. In light of the results of our IUD user survey and the information provided by clinical experts in the project, these recommendations also seem relevant for the German care setting. The 2 non-representative surveys at least suggest that women in Germany are not regularly and often insufficiently informed about IUDs as a contraceptive option. On the other hand, the NICE guideline emphasises the importance of

making an informed and free contraceptive choice with regard to patient autonomy. In the long term, well-informed and completely free decision-making determines adherence to the chosen contraceptive method as well as switching behaviour. In view of high IUD effectiveness, which was confirmed in this HTA report, and their potentially excellent relative cost-effectiveness in Germany, it would be important for IUDs and other long-term contraceptive methods to be regularly discussed as contraceptive options in the German health care setting as well, and for women to be adequately informed about them in order to enable free and informed contraceptive decision-making.

For the UK, the NICE guideline reports low utilization rates of long-term contraceptive methods: around 12% of women aged 16 to 49 use IUDs, compared to 25% each using oral contraceptives and condoms. In Germany, the number of users of long-term contraceptive methods is similarly low. For example, only about 10% of women aged 18 to 49 years use IUDs – compared to 47% using oral contraceptives and 46% using condoms [9]. Simultaneously, the current BZgA survey reports that a marked decrease in oral contraceptive users, especially in the youngest age group, can be observed and that these women express scepticism towards hormone-based contraceptive methods. Against this background, the importance of providing women with high quality, comprehensive information and patient education regarding all available contraceptive methods – as called for by the NICE guideline – appears important for Germany as well.

8.3 HTA report compared to further non-randomised studies

The search for the benefit assessment of the present report was limited to randomised controlled studies. These studies provide the highest certainty of results with regard to the effects that can be causally attributed to the intervention in each case. Nevertheless, other study types may provide further relevant information. For example, clinical registries or prospective cohort studies can be used to assess long-term effects in a larger number of study participants. A review found in the course of the scoping searches summarises the results of such studies with regard to the outcome of ovarian cancer, concluding that the incidence of ovarian cancer might be reduced by 30% via the use of IUDs rather than other, non-IUD methods [106]. Only 1 of the 9 studies analysed in this review included women with copper IUDs, while 2 were on hormonal IUDs. In the remaining 6 studies, the IUD type was not specified.

Comparative intervention studies without active allocation to the intervention groups or cohort studies may also provide evidence regarding risks or side effects, provided they are methodologically sound and controlled for potential confounders. A metaanalysis of such studies, which investigate the question of breast cancer incidence as a result of the insertion of hormonal IUDs, found no association in 4 studies [107].

A retrospective evaluation of a cohort of 10,674 women at Columbia University shows a slightly higher incidence of higher-grade cervical neoplasia in a propensity score-matched analysis, with 2.4 cases (hormonal IUD) versus 5.2 cases (copper IUD) per 1000 subject-years [108]. In contrast, a Danish registry analysis with 60 551 participants arrives at approximately the same incidences for CIN3 or higher lesions in women with initially unremarkable cytology [109].

In summary, non-randomised studies show a slight reduction in the incidence of ovarian cancer under the use of IUDs. Whether this protective effect is higher in hormonal or copper IUDs cannot be deduced with certainty from the available data. With regard to breast cancer and cervical carcinoma incidences, the results are currently less clear.

Another study to be highlighted is EURAS, which investigated the 2 types of IUDs in 61 448 women with regard to possible uterine perforations using a multinational, prospective, non-comparative cohort design. In light of low incidences and predominantly benign courses of disease, no differences were found with regard to this risk (1.4 per 1000 insertions of hormonal IUDs and 1.1 per 1000 insertions of copper IUDs [110]).

8.4 Critical reflection on the approach used

This report assesses the benefit of contraception with copper IUDs in comparison with hormonal IUDs with regard to patient-relevant outcomes, focusing on positive and negative side effects. Likewise, intervention costs, a health economic analysis, and a presentation of ethical, social, legal, and organisational aspects associated with the medical intervention (=the use of IUDs) are to be analysed (see Section 2).

The methodological literature includes studies which take a critical view of summarising harm aspects within the framework of systematic reviews. For example, Chou et al. point out that clinical trials do a very poor job of documenting harm outcomes (operationalization, recording, quality control) [111]. They argue that harm outcomes are often not the primary focus of study authors or reviewers and are consequently recorded far less frequently and completely than benefit outcomes, which are usually defined as primary outcomes. Alongside reporting bias, they therefore see insufficient power as a common problem, preventing a meaningful comparison between the groups with regard to damage outcomes. They argue that because of heterogeneous measurement methods and operationalizations, metaanalyses and the pooling of damage estimates from different studies can solve this problem only in very rare cases.

In the present report, a quantitative synthesis of results (metaanalysis) was likewise impossible. This was due to substantial differences in follow-up periods (1 to 7 years), very heterogeneous outcome operationalization (e.g. "hormonal reasons for discontinuation"), and different analysis methods (timetable methods versus rates at specific time points).

Much better documented are large-scale, prospective, but non-randomised studies [109,112]. However, despite all adjustment efforts, these studies always suffer from the uncertainty whether any identified differences can be causally attributed to the respective IUD type.

Since 8 RCTs enrolling a total of over 10 000 women were found for the research question of the present report, it was possible to derive a hint in some cases. Three of the 8 studies each included over 2500 women, and they used consistent operationalization of harm outcomes and the same follow-up times and analysis methods. In addition, we compared the results of our analysis of the RCTs with those of the large registries, which corroborated the hints we found.

However, 2 characteristics of the 8 included studies are worthy of special attention. As far as could be inferred from the information in the publications, all 8 studies included Mirena-type hormonal IUDs delivering 20 µg levonorgestrel per day. Similarly, 7 out of 8 studies used the T380A type IUD (with a surface area of 380 mm^2) as the copper IUD. Copper chains or copper bead ball products were not included in the comparisons conducted in the studies (see Section A3.2 of the full report). This HTA report did not identify any comparative studies on hormonal IUDs releasing lower quantities of hormones, copper IUDs with lower copper release, or copper chains or copper bead ball products. The results described are therefore of informative value only regarding the products investigated.

IUD manufacturers argue that the newer hormonal IUDs or other types of IUDs such as copper bead balls are often smaller, offer a better fit, and release lower quantities of hormones or copper. According to the manufacturers, they should therefore cause less pain during insertion, especially in young women, and cause fewer side effects. Some hormonal IUDs release significantly lower quantities of hormones and are thus expected to cause fewer hormone-related positive and negative side effects. However, they likely do not work as well against dysmenorrhoea or menstrual bleeding disorders. As it was impossible to find any results from RCTs on these products and dosage forms, no evidence-based conclusions can be drawn on this topic. A smaller RCT on hormonal IUDs with lower hormone delivery rates will soon be finalized [27].

A second peculiarity concerns the women enrolled in the RCTs. Six of 8 studies required a history of at least 1 pregnancy. In the other 2 studies, median parity was 2 to 3. The median parity of all included studies was between 1 and 3, which means that half of the included women had already given birth to 1 to 3 children. The results of the analysed studies are therefore transferable and of informative value only for women with prior pregnancies. Additionally, the median age of the women was between 26.5 and 31.4 years (see Table 14 of the full report). Older or younger women were underrepresented in the studies. Thus, the results are transferable only to a limited extent in this regard as well.

According to the results of the studies included, infection with HIV does not appear to be an effect modifier with regard to the outcomes investigated in this report (effectiveness of contraception; positive and negative side effects). Therefore, the results were analysed together with the other studies.

Further studies on younger or older women or nulliparous women, or even on newer types of IUDs or dosage forms would be helpful to support manufacturers' promises with evidence.

9 Conclusion

The research question of the present HTA report firstly called for an investigation of the benefits of contraception with copper IUDs versus hormonal IUDs in women of childbearing age with a desire or indication for contraception. The focus was on whether the 2 types of IUDs differ in terms of their positive and negative side effects. Further research questions of this report involved the calculation of costs and the evaluation of the cost-effectiveness of contraception with copper IUDs versus hormonal IUDs as well as the review of ethical, social, legal, and organisational aspects associated with the medical interventions.

For this research question, a total of 33 outcomes from 8 randomised controlled trials were assessed and combined into 7 outcome groups. For the outcome group "pregnancy and expulsion" (4 outcomes), a hint of a minor advantage of hormonal IUDs was found regarding the outcome "pregnancies (all)", although both types of IUDs exhibited high contraceptive effectiveness. In the outcome group "effects on menstruation" (6 outcomes), a hint of less frequent occurrence of various bleeding changes was found for copper IUDs (outcomes: "amenorrhoea" and "hypomenorrhoea"). For the outcome "increased menstruation" (hypermenorrhoea or menorrhagia), a hint of more frequent occurrence with copper IUDs was found. In the outcome group "pain", no differences were found regarding the 3 individual outcomes. In the group "inflammations and other complaints" containing 3 individual outcomes, only the outcome "other complaints" showed a hint of less frequent occurrence in copper IUDs. The outcome group "reasons for removal" combined 8 individual outcomes. One ("other, non-IUD-related reasons") showed a hint of less frequent removal of copper IUDs. For the outcome group "health-related quality of life", no difference was found regarding any of the measured dimensions. In addition, results were extracted on 8 outcomes presented as supplementary information, but no conclusions on benefit were derived from them.

All 8 included studies suffer from a high risk of bias due to lack of blinding and some other methodological deficiencies. In addition, all of the hormonal IUDs used in the studies contained 52 mg levonorgestrel, and most of the employed copper IUDs had a surface area of 300 mm^2. Thus, the conclusions of the report are not fully transferable to further developments of the IUDs. Furthermore, the transferability of the available results to younger women (< 18 years) or older women (> 40 years) or to women who have not yet given birth is unclear.

In the foreseeable future, no further studies which might provide relevant results comparing the IUDs or their advancements are expected.

According to the calculations in this report, the total 5-year costs range between €300 and €850 for a hormonal IUD and between €200 and €750 for a copper IUD (see Section 6.1). These estimates include follow-up examinations and IUD removal. The actual costs within the

mentioned ranges depend on the price of the respective IUD, the billing modalities (especially Uniform Value Scale versus the GOÄ), and the age and individual situation of the respective patient. The majority of the costs are generally reimbursed by SHI, provided a woman is younger than 22 years. Women aged 22 years or older must cover almost the entire cost out of pocket.

The cost-effectiveness analysis for both types of IUDs shows them to be cost-effective compared to other contraceptive methods. This is due in particular to their long and comparatively high effectiveness. In the reviewed US and UK models, copper IUDs were typically the most cost-effective contraceptive method or at least among the most cost-effective methods. Hormonal IUDs were slightly more expensive, but also slightly more effective, and therefore also cost-effective. For Germany, the 2 types of IUDs presumably likewise represent comparatively cost-effective contraceptive methods, especially compared to no contraception, condoms, or oral contraceptive pills.

The costs of intrauterine contraceptive methods are mainly incurred directly at insertion. However, they then protect the woman for several years. In contrast, the costs of other contraceptive methods, especially oral contraceptive pills, are spread across quarters or the entire year and therefore do not require as high of an immediate expenditure. This might mean that especially younger women or those who are socioeconomically worse off are more likely to spontaneously opt for a short-term method rather than a long-term one. On the other hand, modelling has shown IUDs to be very cost-effective compared to other contraceptive methods. From an economic point of view, they are therefore a cost-effective alternative both for SHI and for women as self-payers.

The analysis of ethical aspects associated with the 2 types of medical interventions focused on the different positive and negative side effects based on the results from the benefit assessment as well as the determination of costs and the evaluation of cost-effectiveness. The focus here was on their impact on autonomy in the sense of self-determined decision-making in the choice between copper and hormonal IUDs.

Both types of IUDs are suitable for ensuring long-term birth control based on a self-determined decision. In this way, they have an equally (reproductive) autonomy-promoting effect. Both types of IUDs are also associated with aspects which may limit reproductive autonomy. For example, women may delay the insertion or removal of the IUD because of external influences, fear of pain, or the associated costs. Such aspects may limit the free will to initiate or continue long-term contraception and thus birth control.

Particularly the different positive and negative side effects mean that the decision in favour of a copper or hormonal IUD is preference sensitive. Making a self-determined decision requires that the necessary information about the types of IUDs is available. Lack of

information may, for instance, lead to a woman having an IUD removed prematurely because of false expectations. In this case, 2 invasive procedures, possibly involving pain, are conducted which could have been avoided. Self-determined decision-making requires comprehensive information and counselling on the expected benefits as well as on positive and negative side effects.

When analysing the social aspects associated with the medical interventions, questions about access and affordability of these contraceptive methods may be extracted from the identified literature. The identified publications consistently indicate that the decision in favour of a contraceptive method is highly dependent on social and cultural norms and values as well as individual life circumstances and preferences ("preference-sensitive decision"). The survey of affected women also suggests that women perceive and evaluate particularly the bleeding-related positive and negative side effects of IUDs very differently. For example, some women welcome the decrease or absence of menstruation, while others experience it as frightening and unnatural.

For these reasons, it is necessary to inform women and couples in a comprehensive, understandable, and balanced way about the benefits and positive and negative side effects of all available contraceptive methods in order to enable "woman-centred contraception" in the sense of shared decision making.

With regard to the legal aspects associated with the medical interventions, hormonal IUDs are medicinal products, whereas copper IUDs are medical devices. In this respect, different procedural standards apply to the approval of these IUDs. In the case of a defective IUD, this results in different bases for women's claims for compensation.

The 2 types of IUDs do not differ in terms of the conclusion of the treatment contract, patient information, or consent to the intervention.

The fact that the costs for both IUD types are reimbursed by SHI funds up to the age of 22 years and are then self-pay is based on social legislation.

Conclusion in terms of addressing the concerns of those proposing the topic:

Overall, this HTA report demonstrates that hormonal IUDs and copper IUDs are comparatively highly reliable and long-acting contraceptive methods that differ only slightly in terms of their effectiveness in preventing pregnancy and their positive and negative side effects. How these differences are evaluated depends on the respective woman’s values and preferences and her situation in life. Since the choice of contraceptive is a preference-sensitive decision, it is necessary to provide complete information which covers all contraceptive methods, is correct in terms of content, and is comprehensible for the general public. This is necessary to enable women to make informed, autonomous decisions which represent the best possible

alternative for them individually. Not only benefits and positive and negative side effects, but also the associated costs, the respective reimbursement situation, cost-effectiveness as well as ethical, social, and organisational aspects must always be transparently addressed.

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Please see full HTA report for the full reference list.

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The full HTA report (German version) is published under

https://www.iqwig.de/sich-einbringen/themencheck-medizin/berichte/ht21-05.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [142] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 7 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 7: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Section 3.2; Chapter 4
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.3; Chapter 6
Ethical analysis (ETH)	**Ethical aspects** Section 3.4; Section 7.1
Patients and social aspects (SOC)	**Social aspects** Section 3.5; Section 7.2
Legal aspects (LEG)	**Legal aspects** Section 3.5; Section 7.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.5; Section 7.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1 – Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to October 05, 2021

The following filter was adopted:

- Systematic review: Wong [113] – High specificity strategy

#	Searches
1	Intrauterine Devices, Copper/
2	((intrauterine device* or IUD*) and copper*).ti,ab.
3	long-acting reversible contraception*.ti,ab.
4	or/1-3
5	cochrane database of systematic reviews.jn.
6	(search or MEDLINE or systematic review).tw.
7	meta analysis.pt.
8	or/5-7
9	8 not (exp animals/ not humans.sh.)
10	and/4,9
11	10 and (english or german).lg.

2. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	("Intrauterine Devices")[mh]
2	intrauterine device* OR IUD*
3	long-acting reversible contraception*
4	#3 OR #2 OR #1

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to December 16, 2021

The following filter was adopted:

- RCT: Lefebvre [114] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	Intrauterine Devices, Copper/
2	((intrauterine device* or contraceptive device* or IUD*) and (copper* or ?cu*)).ti,ab.
3	or/1-2
4	Intrauterine Devices, Medicated/
5	exp Norgestrel/
6	Progesterone/
7	(levonorgestrel* or LNG or progest*).ti,ab.
8	or/4-7
9	randomized controlled trial.pt.
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly or trial or groups).ab.
12	drug therapy.fs.
13	or/9-12
14	13 not (exp animals/ not humans.sh.)
15	and/3,8,14
16	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
17	hi.fs. or case report.mp.
18	or/16-17
19	15 not 18
20	19 and (english or german or multilingual or undetermined).lg.

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations December 16, 2021

#	**Searches**
1	((intrauterine device* or contraceptive device* or IUD*) and (copper* or ?cu*)).ti,ab.
2	(levonorgestrel* or LNG or progest*).ti,ab.
3	and/1-2
4	(clinical trial* or random* or placebo).ti,ab.
5	trial.ti.
6	or/4-5
7	and/3,6
8	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
9	hi.fs. or case report.mp.
10	or/8-9
11	7 not 10
12	11 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2021 December 16

The following filter was adopted:

- RCT: Wong [113] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	copper intrauterine device/
2	((intrauterine device* or contraceptive device* or IUD*) and (copper* or ?cu*)).ti,ab.
3	or/1-2
4	levonorgestrel releasing intrauterine system/
5	Norgestrel/
6	Levonorgestrel/
7	Progesterone/
8	(levonorgestrel* or LNG or progest*).ti,ab.
9	or/4-8
10	(random* or double-blind*).tw.
11	placebo*.mp.
12	or/10-11
13	and/3,9,12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	16 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2021

#	Searches
#1	[mh ^"Intrauterine Devices, Copper"]
#2	((intrauterine device* or contraceptive device* or IUD*) and (copper* or ?cu*)):ti,ab
#3	#1 or #2
#4	[mh ^"Intrauterine Devices, Medicated"]
#5	[mh "Norgestrel"]
#6	[mh ^"Progesterone"]
#7	(levonorgestrel* or LNG or progest*):ti,ab
#8	#4 or #5 or #6 or #7
#9	#3 and #8
#10	#9 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#11	#10 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#12	#11 in Trials

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
(intrauterine device OR contraceptive device OR IUD) AND (copper OR CU)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(copper* OR CU) AND (intrauterine device* OR contraceptive device* OR IUD*)

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to January 20, 2022

The following filter was adopted:

- Health economic evaluation: Glanville [115] – Emory University (Grady) filter

#	**Searches**
1	Intrauterine Devices, Copper/
2	((intrauterine device* or contraceptive device* or IUD*) and (copper* or ?cu*)).ti,ab.
3	or/1-2
4	Intrauterine Devices, Medicated/
5	exp Norgestrel/
6	Progesterone/
7	(levonorgestrel* or LNG or progest*).ti,ab.
8	or/4-7
9	(economic$ or cost$).ti.
10	cost benefit analysis/
11	treatment outcome/ and ec.fs.
12	or/9-11
13	12 not ((animals/ not humans/) or letter.pt.)
14	and/3,8,13
15	14 not (comment or editorial).pt.
16	15 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2022 January 20

The following filters were adopted:

- Health economic evaluation: Glanville [115] – Embase G

#	Searches
1	copper intrauterine device/
2	((intrauterine device* or contraceptive device* or IUD*) and (copper* or ?cu*)).ti,ab.
3	or/1-2
4	levonorgestrel releasing intrauterine system/
5	Norgestrel/
6	Levonorgestrel/
7	Progesterone/
8	(levonorgestrel* or LNG or progest*).ti,ab.
9	or/4-8
10	(cost adj effectiveness).ab.
11	(cost adj effectiveness).ti.
12	(life adj years).ab.
13	(life adj year).ab.
14	qaly.ab.
15	(cost or costs).ab. and controlled study/
16	(cost and costs).ab.
17	or/10-16
18	and/3,9,17
19	18 not medline.cr.
20	19 not (exp animal/ not exp human/)
21	20 not (Conference Abstract or Conference Review or Editorial).pt.
22	21 and (english or german).lg.

3. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	("Intrauterine Devices")[mh]
2	intrauterine device* OR IUD*
3	long-acting reversible contraception*
4	#3 OR #2 OR #1