Ultrasound for fracture diagnosis in children with a suspected long tubular bone fracture of the upper limbs[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

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 A8 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Meinrad Beer, University Hospital Ulm, Ulm

IQWiG thanks the external expert for his collaboration in the project.

Patient and family involvement

Patients or family members were consulted during the preparation of the report. Two people participated in the discussion. Its aim was to obtain information on the following topics: experiences, wishes and concerns regarding the diagnostic procedures, impact of the disease, and coping with the disease. IQWiG would like to thank the participants for taking part in the discussion. They not involved in the actual writing of the report.

IQWiG employees

- Martina Lietz
- Benjamin Becker
- Lars Beckmann
- Thorsten Busan
- Tatjana Hermanns
- Britta Runkel
- Stefan Sauerland

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Key statement

Research question

The aim of the present investigation is to assess the benefit of primary sonographic diagnostics ("ultrasound") compared to primary radiological standard diagnostics ("X-ray") in children with a suspected fracture of a long tubular bone of the upper limbs. The focus of the assessment was on patient-relevant outcomes.

Conclusion

A total of 28 test accuracy studies on ultrasound and 1 randomized controlled trial (RCT) on the diagnostic-therapeutic chain were assessed. The meta-analysis of these 28 studies showed that overall, the sensitivity of ultrasound was safely above the required minimum level of 90% for all relevant fracture sites (forearm, elbow and upper arm). Sensitivity analyses considering these 3 fracture sites each showed a similar result for sensitivity.

In children with a suspected distal forearm fracture, the RCT confirmed that ultrasound reduces radiation exposure (indication of greater benefit), has no functional disadvantages (hint of non-inferiority), and also shows comparable results for other morbidity outcomes. Therefore, the overall assessment of test accuracy and patient-relevant outcomes in children with a suspected distal forearm fracture provides proof of a greater benefit of ultrasound versus X-ray.

In children with a suspected elbow fracture, overall, there is an indication of a greater benefit on the basis of the test accuracy studies.

In children with a suspected fracture of the upper arm, overall, there is only a hint of a greater benefit. This is due to an evidence base of only 168 people, combined with an imprecise sensitivity estimate (lower limit of the 95% confidence interval: about 72%). Due to the weaker evidence underlying the benefit assessment, a confirmatory cohort study should be considered for the fracture site "non-distal upper arm". Therefore, the key points of a potential testing study were outlined for this fracture site.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
A+E	accident and emergency (department)
AE	adverse event
CI	confidence interval
FPS-R	Faces Pain Scale – Revised
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
IDR	incidence density ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LRT	likelihood ratio test
MD	mean difference
Med-D	median difference
OR	odds ratio
POCUS	point-of-care ultrasound
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
Q	quartile
QALYs	quality-adjusted life years
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SR	systematic review

1 Background

Injuries to the musculoskeletal system are common in childhood and only around half of children remain fracture-free throughout their growth [1]. Therefore, one of the most common reasons why children and adolescents seek medical treatment, usually as an emergency, is a suspected bone fracture [2]. The annual incidence of a fracture is around 100 to 350 per 100,000 children, depending on the age group [3]. In Germany, boys are affected almost twice as often as girls. Sports and traffic accidents account for around half of all cases. Approximately 80% of paediatric fractures affect the upper limbs, with the distal forearm being the most commonly injured [3].

If there is sufficient suspicion of a fracture, standard radiological diagnostics are routinely performed [4]. X-rays of the limbs are associated with a comparatively low mean effective radiation dose. However, as children are more sensitive to radiation and have a higher risk of being exposed to cumulative radiation doses over time [5,6], especially in this age group, it is important to avoid radiological diagnostics as much as possible.

Ultrasound (also called sonography) as a diagnostic imaging test for the detection or exclusion of fractures ("fracture ultrasound") has gained increasing interest over the last 25 years due to technical developments and increasing accuracy [7]. A recent German survey showed that almost a quarter of all doctors in accident and emergency departments (A+E) already use fracture ultrasound [8]. A German S1 guideline states that, with appropriate expertise and acceptance, ultrasound alone can be sufficient in children and adolescents to exclude or detect a non-displaced or tolerably displaced forearm fracture that certainly does not require surgical treatment [9,10]. In addition to avoiding an X-ray, another practical advantage is that children can be accompanied by their parents during ultrasound - in contrast to an X-ray. The transducer can also move around the arm while it is in a low-pain relief position. By avoiding movement of the arm, ultrasound could therefore be perceived as less painful than X-ray [11]. Further practical advantages result from the wider range of applications, especially directly in A+E or even outside medical facilities, for example directly at the accident site.

2 Research question

The aim of the present investigation is to assess the benefit of primary sonographic diagnostics compared to primary radiological standard diagnostics in children with a suspected fracture of a long tubular bone of the upper limbs. The focus of the assessment was on patient-relevant outcomes.

3 Methods

The target population of the benefit assessment consisted of children with a suspected fracture of a long tubular bone of the arm. The test intervention for fracture diagnosis was primary ultrasound. The control intervention was primary X-ray. “Primary” refers to the initial diagnostic procedure to detect a suspected fracture.

The following patient-relevant outcomes were to be considered for the investigation:

- morbidity (in particular arm function, pain, etc.)
- health-related quality of life
- (serious) adverse events ([S]AEs)

Radiation exposure was to be recorded as a further outcome.

Only randomized controlled trials (RCTs) were to be included in the benefit assessment. There was no restriction regarding the duration of the study.

If RCTs of the diagnostic-therapeutic chain were not available or not available in sufficient quantity and quality for the benefit assessment, an assessment based on diagnostic cohort studies was considered.

In parallel to the preparation of the protocol (“report plan”), a search for systematic reviews (SRs) was conducted in the MEDLINE database (also includes the Cochrane Database of Systematic Reviews) and the International Health Technology Assessment (HTA) Database, as well as on the websites of National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was examined whether at least 1 high-quality and current SR was available for each research question whose information retrieval could be used as the basis for the assessment (hereinafter: basic SR).

If such a basic SR was available, a supplementary search for studies for the period not covered by the basic SR was carried out in a second step. Otherwise, the search for studies was carried out without restricting the search period.

The systematic literature search for studies was conducted in the databases MEDLINE, Embase and Cochrane Central Register of Controlled Trials.

In addition, the following information sources were considered: study registries, documents submitted by the Federal Joint Committee (G-BA), reference lists, author enquiries, and documents provided from hearing procedures.

The selection of relevant studies was carried out by 2 persons independently of each other. Discrepancies were resolved by discussion. Data were extracted into standardized tables. Across-outcome and outcome-specific risk-of-bias criteria were assessed to assess the qualitative certainty of results (shortened to “certainty of results” in the following text), and the risk of bias was rated as low or high in each case. The results of the individual studies were described according to outcomes.

In addition to the comparison of the results of the individual studies, meta-analyses and sensitivity analyses were performed and effect modifiers examined, provided that the methodological requirements were met.

For each outcome, a conclusion on evidence of (greater) benefit and (greater) harm was made in 4 grades regarding the respective certainty of conclusions: either proof (highest certainty of conclusions), an indication (moderate certainty of conclusions), a hint (weakest certainty of conclusions), or none of these 3 situations was present. The latter case occurred when no data were available or the available data did not allow any of the other 3 conclusions. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

Finally, an assessment of benefit and harm across outcomes was performed.

In cases where there was no hint of (greater) benefit or (greater) harm, a conclusion was drawn on the potential of the intervention in terms of a necessary treatment alternative and corresponding key points of a testing study were formulated.

In the case that no RCT on the diagnostic-therapeutic chain could be identified, for the present research question it was possible to conduct a benefit assessment based on results on sensitivity from test accuracy studies instead.

The data were extracted into standardized tables. In the assessment based on diagnostic cohort studies, in addition to the evaluation of the certainty of results at the study level, an assessment of concerns regarding the transferability of the results was carried out on the basis of the risk of bias. The results of the individual studies on test accuracy were summarized meta-analytically in a bivariate model. The results were presented in tabular and graphical form. In addition to the overall analysis with all available data, sensitivity analyses were performed with regard to fracture site, risk of bias and consideration of the results from follow-up X-rays as a reference standard.

4 Results

4.1 Results of information retrieval

No SR was considered as a basic SR for the purpose of identifying primary studies.

The systematic literature search identified an RCT on the diagnostic-therapeutic chain relevant to the research question, for which only 1 registry entry and 2 publications (study protocol publication [12] and statistical analysis plan [SAP] [13]) were available at the time of information retrieval for the preliminary report. In the further course of the project, 1 publication with results on this RCT (Snelling 2023 [14]) was published, which is now used for the final report.

With regard to studies on test accuracy, the information retrieval revealed 28 relevant diagnostic cohort studies. One ongoing study was identified. In addition, 4 studies with unclear status and 2 completed studies without reported results were identified.

The search strategies for bibliographic databases and study registries can be found in the appendix. The last search took place on 15 August 2023.

Table 1: Study pool of the benefit assessment

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / results report from study registry**	**Study report from manufacturer (not public)**	**Other documents**
RCTs				
BUCKLED RCT (Snelling 2023)	Yes [14]	Yes [15] / no	No	Yes [12,13]
Diagnostic cohort studies				
Ackermann 2010	Yes [16]	No / no	No	No
Ahmed 2018	Yes [17]	No / no	No	No
Akinmade 2019	Yes [18]	No / no	No	No
Aziskhani 2022	Yes [19]	No / no	No	No
Chaar-Alvarez 2011	Yes [20]	No / no	No	No
Chen 2007	Yes [21]	No / no	No	No
Eckert 2012a	Yes [22]	No / no	No	No
Eckert 2012b	Yes [23]	No / no	No	No
Eckert 2013	Yes [24]	No / no	No	No
Eckert 2014a	Yes [25]	No / no	No	No
Eckert 2014b	Yes [26]	No / no	No	No
Epema 2019	Yes [27]	No / no	No	No
Galletebeitia 2019	Yes [28]	No / no	No	No
Hedelin 2017	Yes [29]	No / no	No	No
Herren 2015	Yes [30]	No / no	No	No
Ko 2019	Yes [31]	Yes [32] / yes	No	No
Moritz 2008	Yes [33]	No / no	No	No
Pistor 2003	Yes [34]	No / no	No	No
Poonai 2017	Yes [35]	No / no	No	No
Rabiner 2013	Yes [36]	No / no	No	No
Rowlands 2017	Yes [37]	Yes [38] / no	No	No
Sinha 2011	Yes [39]	No / no	No	No
Snelling 2021	Yes [40-42]	Yes [43] / no	No	No
Snelling 2022	Yes [44]	No / no	No	No
Tandogan 2015	Yes [45]	No / no	No	No
Tokarski 2018	Yes [46]	No / no	No	No
Varga 2021	Yes [47]	No / no	No	No
Williamson2000	Yes [48]	No / no	No	No
RCT: randomized controlled trial				

4.2 Results of studies on the diagnostic-therapeutic chain

4.2.1 Characteristics of the study on the diagnostic-therapeutic chain included in the assessment

The multicentre study BUCKLED RCT (Snelling 2023 [12-14]) from Australia included 270 children between 5 and 15 years of age with a suspected distal forearm fracture. Randomization was stratified 1:1 according to location (study centre) and age (5 to 9 years and 10 to 15 years). Exclusion criteria included obvious angulation, injury older than 48 hours, a compound or open fracture, or congenital malformation of the forearm (see also Table 15 of the full report). The ultrasound examinations were performed by healthcare professionals (emergency physicians, physiotherapists, nurse practitioners and other healthcare professionals). In preparation for the study, they received a 2-hour training programme on a phantom arm model, ultrasound scanning training of 20 patients with buckle or cortical fractures, ultrasound interpretation exercises using case examples and a final assessment of their practical ultrasound skills to obtain a qualification certificate.

As part of the study, the children in the intervention group were scanned with a mobile ultrasound device (point-of-care ultrasound [POCUS]) in 6 views. In the POCUS group, a distinction was made between the categories "no fracture", "buckle fracture" and "other fracture" for the ultrasound diagnosis; if the result was "no fracture" or "buckle fracture", no subsequent X-ray was performed. If the result was "other fracture", an X-ray was performed. An X-ray was also performed in the event of unusually severe pain or if there were other signs indicating a fracture. Subsequent patient management was then based on the X-ray diagnosis.

In the control group, the X-rays were performed in at least 2 planes. The X-ray and POCUS images were analysed at a later date by a panel of experts to correctly classify fractures, among other things.

The average age in the intervention group was 10.4 ± 2.8 (standard deviation) years; in the control group, it was 10.2 ± 2.8 years. The proportion of boys was 49.6% in the intervention group and 57.0% in the control group.

4.2.2 Overview of the patient-relevant outcomes of the study on the diagnostic-therapeutic chain

Data on patient-relevant outcomes were extracted from the Snelling 2023 publication [14] on the BUCKLED RCT (Table 1).

For the outcome category of morbidity, usable data on arm function were available, collected with the validated Patient-Reported Outcomes Measurement Information System (PROMIS) paediatric short questionnaire to assess upper limb function [49-52]. In the following, this outcome is referred to simply as "arm function". The analysis after 4 weeks was considered the primary outcome by the study author team. Furthermore, the number of missed school days (within 4 or 8 weeks) was analysed.

In addition, usable data on the outcome of pain was also available for the outcome category “morbidity” with analyses after 1, 4 and 8 weeks, collected using the "6-Point Faces Pain Scale - Revised" (FPS-R) instrument.

With regard to the outcome of radiation exposure, results were reported on the frequency of X-rays performed.

No results were reported on the outcome of health-related quality of life in Snelling 2023 [14], but according to the SAP [13] and study protocol publication [12], the recording of this outcome is explicitly planned in connection with a health economic evaluation, which is not included in Snelling 2023 [14]. With the help of a generic quality of life instrument - the Child Health Utility 9D (CHU9D) questionnaire - the determination of quality-adjusted life years (QALYs) is planned.

For the outcome category of adverse effects, usable data on AEs and complications and on unplanned reattendances to A+ E were collected initially and after 8 weeks.

Furthermore, patient satisfaction and the satisfaction of accompanying parents were also reported, which are presented here as supplementary information.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes						
	Morbidity				HRQoL	Adverse effects	
	Arm function	Pain	Radiation exposure[a]	Return to normal activities[b]	Health-related quality of life[c]	Complications	Unplanned reattendance to A + E
BUCKLED RCT (Snelling 2023)	●	●	●	●	x	●	●

●: Data were reported and were usable.
x: Data were not reported despite planned collection.
a. Operationalized as frequency of X-rays.
b. Operationalized as missed school days.
c. Recorded using the Child Health Utility 9D (CHU9D) questionnaire; analysed at 1, 4 and 8 weeks; later publication of data expected.
A+E: accident and emergency department; HrQoL: health-related quality of life

4.2.3 Assessment of the risk of bias of the results of the study on the diagnostic-therapeutic chain

Despite the lack of blinding of children and health care staff, the risk of bias was classified as low across all outcomes, as the lack of blinding was not expected to affect the treatment results via differential differences in treatment (performance bias).

4.2.4 Results on patient-relevant outcomes of the study on the diagnostic-therapeutic chain

4.2.4.1 Results on arm function

Usable data was available on the outcome of arm function at 1, 4 and 8 weeks. Arm function was assessed using PROMIS (see Section 4.2.2), with a specified range of 8 to 40, with higher scores indicating better function (Snelling 2023 [14]). Snelling 2023 tested for non-inferiority of ultrasound, with a difference of -5 points as the non-inferiority threshold. The non-inferiority threshold of -5 points was determined by expert consensus in the BUCKLED RCT study group.

The intention-to-treat (ITT) analyses of the 3 analysis times were used for the present assessment. The result at 4 weeks (as the primary outcome) was a mean score of 0.1 points (95% confidence interval [95% CI]): [-1.3; 1.4]). The corresponding results for 1 week and 8

weeks were 0.5 (95% CI: [−1.6; 2.6]) and 0.2 (95% CI: [-0.3; 0.8]), respectively (see also Table 19 of the full report). For all 3 analysis times, the lower CI limits were clearly above the non-inferiority limit of -5 points. The point estimates were close to zero, numerically in favour of ultrasound (see also Table 19 of the full report). Even if a markedly lower non-inferiority threshold had been set, e.g. -2 points, the non-inferiority of ultrasound would have been shown, as the lower 95% CI limits ranged between -1.6 and -0.6.

Subgroup analysis for age

In Snelling 2023, a subgroup analysis for age was carried out with regard to the outcome of arm function, for which the children were divided into the age groups 5 to 9 years and 10 to 15 years. The test for interaction did not produce a statistically significant result (p-value: p = 0.052), even though the I^2 measure is very high at 73.4%. However, the results for both age groups are clearly above the non-inferiority threshold of -0.5 with their lower 95% CI limit (see Figure 3 of the full report). To summarize, there is no reason for a separate analysis by age group.

Conclusion on benefit with regard to arm function

As the PROMIS short questionnaire is a patient-reported outcome (PRO), a high overall risk of bias can be assumed for the results on the outcome "arm function" due to the complete lack of blinding (see also Table 18 of the full report). The results for this outcome were therefore classified as having moderate certainty. In terms of numbers, the results were certainly in a range that excludes a relevant disadvantage of ultrasound. Thus, in the overall assessment of distal forearm fractures, a hint of non-inferiority of ultrasound versus X-ray is derived with regard to arm function.

4.2.4.2 Results on pain

Data were available for the outcome of pain at the analysis times of 1, 4 and 8 weeks. Data on pain occurring in connection with the diagnostic procedure were not collected. Data were collected using the validated FPS-R instrument (0 to 10 points, in 6 steps of 2 points each [53,54]), with higher scores indicating greater pain. The result of the ITT analyses was: mean difference (MD) at 1 week: 0.0 points (95% CI: [-0.6; 0.5]; p > 0.999 [IQWiG's own calculation, asymptotic]); at 4 weeks: 0.1 points (95% CI: [-0.28; 0.48]; p = 0.606 [IQWiG's own calculation, asymptotic]); and at 8-weeks: -0.2 points (95% CI: [-0.5; 0.1]; p = 0.192 [IQWiG's own calculation, asymptotic]) (see also Table 20 of the full report).

Conclusion on benefit with regard to pain

As the FPS-R is a PRO, a high overall risk of bias for the results on the outcome of pain can be assumed due to the complete lack of blinding (see also Table 18 of the full report). The results for this outcome were therefore classified as having moderate certainty. Overall, for distal

forearm fractures, no hint can be derived for a greater benefit or harm of ultrasound versus X-ray with regard to the outcome of pain.

4.2.4.3 Results on radiation exposure

For the outcome "radiation exposure", which is to be considered a valid surrogate outcome in the context of morbidity (also due to legal requirements), usable data were available at the time of the initial diagnostic procedure and at the time of follow-up (aftercare) of up to 8 weeks. Radiation exposure was operationalized as the frequency of X-rays.

The ITT analysis of the frequency of X-rays at the time of the initial diagnostic procedure showed a statistically significant effect in favour of ultrasound versus X-ray, with an incidence density ratio (IDR) of 0.33 (95% CI: [0.27; 0.40]; $p < 0.001$ [IQWiG's own calculation, asymptotic]). According to the study protocol, no children - regardless of the diagnostic procedure they were randomized to - were allowed to have an ultrasound during follow-up; they underwent an X-ray, if necessary. The frequency of X-rays that were only performed as part of the follow-up / aftercare up to 8 weeks in both groups (i.e. not at the time of the initial diagnostic procedure), showed no statistically significant result when comparing ultrasound with X-ray (IDR = 0.91; 95% CI: [0.48; 1.73]; $p = 0.773$ [IQWiG's own calculation, asymptotic]), whereby the point estimate is numerically in favour of ultrasound (see also Table 21 of the full report).

Conclusion on benefit with regard to radiation exposure

The results of the initial diagnostic procedure are decisive for the assessment as the point in time at which ultrasound should be used according to the research question. As the results on radiation exposure had a low risk of bias at the outcome level (see also Table 18 of the full report) and were therefore considered to be of high certainty, overall, an indication of a greater benefit of ultrasound versus X-ray can be inferred for distal forearm fractures.

4.2.4.4 Results on return to normal activities

For the outcome "return to normal activities" in the morbidity category, usable data was available at 4 and 8 weeks, operationalized as missed school days. It can be assumed that a lack of ability to go to school following an arm injury corresponds to a markedly reduced level of the child's physical function. This operationalization of the outcome is therefore patient-relevant.

The ITT analysis of missed school days at 4 weeks showed a statistically significant effect in favour of ultrasound versus X-ray with a median difference (Med-D) of -0.5 (95% CI: [-0.9; -0.1]). The ITT analysis of missed school days at 8 weeks showed no statistically significant result when comparing ultrasound with X-ray, with a Med-D of 0.0 (95% CI: [-0.4; 0.4]).

Conclusion on benefit with regard to return to normal activities

Since the decision to send a child back to school is at least partly at the subjective discretion of the parents, overall, a high risk of bias can be assumed at the outcome level for the results on missed school days (see also Table 18 of the full report). The results for this outcome were therefore classified as having moderate certainty. There was a statistically significant effect in favour of ultrasound, but the Med-D of half a day of missed school is not relevant. Therefore, in the overall assessment of the outcome "return to normal activities", operationalized as missed school days, no hint of a greater benefit or harm of ultrasound versus X-ray was derived.

4.2.4.5 Results on adverse effects

For the outcome category “adverse effects”, usable data were available for the outcomes of AEs or complications and unplanned reattendance to A+E. The reasons for the latter were not fully specified. However, it can be assumed that such reattendance was preceded by an AE or complication and can be considered representative of an AE. Therefore, these results are also included in the adverse effects category and used for the assessment.

In principle, the data on AEs and complications appear to have been systematically collected in the study; this is indicated by the lists of possible complications in the SAP [13] and study protocol publication [12]. However, these are limited to events that are related to the fracture that occurred (e.g. rate of re-injury, increase in deformity, delayed fracture healing, growth disturbance or need for surgical intervention), so that these events are to be understood as complications rather than general AEs, which by definition do not have to be related to the fracture that occurred. In this context, the study protocol publication [12] for the BUCKLED RCT also explicitly refers to complications to be recorded and not to AEs.

The ITT analysis of complications showed 1 child with an event in the ultrasound group (a fall on the fractured arm with change in treatment due to worsening of the fracture) and 2 children with an event in the X-ray group (1 child with a fall on the fractured arm with change in treatment due to worsening of the fracture; 1 child with persistent pain to such an extent that a plaster cast was necessary); there was no statistically significant result in the comparison of ultrasound with X-ray with an odds ratio (OR) of 0.50 (95% CI: [0.04; 5.54]; p = 0.57).

The ITT analysis of unplanned reattendance to A+E showed no statistically significant result when comparing ultrasound with X-ray, with an OR of 0.61 (95% CI: [0.19; 1.92]; p = 0.40). This analysis included 5 children with an event in the ultrasound group and 8 children with an event in the X-ray group.

Conclusion on benefit with regard to adverse effects

For the outcome "complications", a low risk of bias can be assumed (see also Table 18 of the full report). The results for this outcome were therefore classified as having high certainty. For the outcome “unplanned reattendance to A+E”, a high risk of bias for the results can be assumed, as the decision to reattend A+E with the child is at least partly at the subjective discretion of the parents. The results for this outcome were therefore classified as having moderate certainty. Overall, no hint of a greater benefit or harm of ultrasound versus X-ray can be derived for either outcome.

4.2.4.6 Supplementary presentation of the results on patient satisfaction

Analysable data was available on the outcome “patient satisfaction” at 4 and 8 weeks. This outcome was assessed both by the child concerned and by the accompanying parent using a 5-point Likert scale (score range 1 to 5 points), with lower scores indicating greater satisfaction. However, these results are only presented as a supplement and no benefit is derived from them.

The ITT analysis of parent satisfaction showed a statistically significant effect as a mean difference (MD) -0.19 (95% CI: [-0.37; -0.01]; p = 0.040 [IQWiG’s own calculation, asymptotic]) as well as a statistically significant effect at 8 weeks in favour of ultrasound versus X-ray with an MD of -0.20 (95% CI: [-0.35; -0.06]; p = 0.007 [IQWiG’s own calculation, asymptotic]).

The ITT analysis of child satisfaction also showed a statistically significant effect in favour of ultrasound versus X-ray at 8 weeks with an MD of -0.17 (95% CI: [-0.33; -0.01]; p = 0.038 [IQWiG’s own calculation, asymptotic]). The corresponding results at 4 weeks were not statistically significant, with an MD of -0.15 (95% CI: [-0.36; 0.06]; p = 0.163 [IQWiG’s own calculation, asymptotic]); the point estimate is numerically in favour of ultrasound.

This means that 3 out of 4 analyses of child and parent satisfaction showed statistically significant effects in favour of ultrasound versus X-ray (see also Table 24 of the full report). It can be assumed that the results correlate closely.

4.2.4.7 Summarized assessment of the results of the study on the diagnostic-therapeutic chain

Evidence map for studies of the diagnostic-therapeutic chain

The following Table 3 shows the evidence map with regard to the patient-relevant outcomes of the BUCKLED RCT.

Table 3: Evidence map with regard to patient-relevant outcomes

Study	Outcomes						
	Morbidity				HRQoL	Adverse effects	
	Arm function	Pain	Radiation exposure[a]	Return to normal activities[b]	Health-related quality of life[c]	Complications	Unplanned reattendance to A + E
BUCKLED RCT (Snelling 2023)	⇗	⇔	⇑	⇔	–	⇔	⇔

⇑: Indication of a greater benefit of ultrasound versus X-ray.
⇗: Hint of non-inferiority of ultrasound versus X-ray.
⇔: No hint of greater benefit or harm of ultrasound versus X-ray.
-: No data reported.
a. Operationalized as frequency of X-rays.
b. Operationalized as missed school days.
c. According to the SAP [13], the collection of HRQoL data was only planned in connection with a health economic evaluation (namely for the calculation of QALYs), which was not part of Snelling 2023 [14].

HrQoL: health-related quality of life; QALYs: quality-adjusted life years; SAP: statistical analysis plan.

Assessment of the extent of unpublished data

No relevant study on the diagnostic-therapeutic chain without reported results was identified (see Section A3.1.4 of the full report). Therefore, there was no restriction of the certainty of conclusions for this study type.

Weighing of benefits and harms

The study investigated ultrasound in children with a suspected distal forearm fracture. The conclusions on benefit therefore relate to this fracture site.

In terms of radiation exposure, there was an indication that ultrasound was more beneficial than X-ray; at the same time, there was a hint that ultrasound was not inferior with regard to arm function. The results on pain (no statistically significant difference) and return to normal activities (no relevant difference) do not call into question the overall positive benefit-harm ratio.

For the outcomes in the adverse effects category, there were some signs that the AEs may not have been fully recorded and that the reported events should rather be understood in terms of complications. However, ultrasound as a diagnostic procedure can be assumed to have a very low risk of harm. Therefore, the certainty of conclusions is not downgraded.

Overall, with regard to studies on the diagnostic-therapeutic chain, across outcomes, an indication of a greater benefit of ultrasound versus X-ray can be derived for the fracture site of the distal forearm, based on the outcome of radiation exposure.

4.3 Results on diagnostic accuracy studies

4.3.1 Characteristics of diagnostic accuracy studies included in the assessment

Of the 28 studies that reported usable results for the benefit assessment, data were available from 3245 children. These studies included between 17 and 419 children with suspected upper limb fractures and were conducted worldwide between 1997 and 2020.

The most important characteristics are presented in tabular form below, indicating the respective fracture site investigated (for further characteristics of the studies, the index and reference test, the inclusion criteria and the study populations, see Tables 25-28 of the full report).

Table 4: Characteristics of the included diagnostic accuracy studies (multipage table)

	Study	Study design	Patient number N (analysed)	Fracture site	Child age in years Mean (SD)
Diagnostic cohort studies					
1	Ackermann 2010 [16]	Prospective, multicentre	33	Proximal upper arm	7.6 (n.d.)
2	Ahmed 2018 [17]	Prospective, single-centre	42	Forearm	7.2 (n.d.)
3	Akinmade 2019 [18]	Prospective,	39[a]	Fore- und upper arm[a]	5.62 (1.61)
4	Azizkhani 2022 [19]	Prospective, multicentre	75	Elbow	6.51 (3.68)
5	Chaar-Alvarez 2011 [20]	Prospective, single-centre	103	Distal forearm	10.3 (4.3)
6	Chen 2007 [21]	Prospective, single-centre	68	Forearm	10 (n.d.)
7	Eckert 2012a [22]	Prospective, single-centre	115	Forearm	9.1 (n.d.)
8	Eckert 2012b [23]	Prospective	76	Forearm	8.8 (1–14)[b]
9	Eckert 2013 [24]	Prospective	67	Elbow	6 (1–13)[b]
10	Eckert 2014a [25]	Prospective	79	Elbow	6.5 (1.2–13)[b]
11	Eckert 2014b [26]	Prospective, single-centre	106	Elbow[c]	5.9 (1–13)[b]
12	Epema 2019 [27]	Prospective, single-centre	100	Distal forearm	9 (3.6)
13	Galletebeitia 2019 [28]	Prospective, single-centre	115	Forearm	9.1 (3.1)
14	Hedelin 2017 [29]	Prospective, single-centre	116	Distal forearm [d]	11[e] (3–16)[b]
15	Herren 2015 [30]	Prospective, multicentre	201	Distal forearm	9.5 (n.d.)
16	Ko 2019 [31]	Prospective	51	Distal forearm	9.9 (2.6)
17	Moritz 2008 [33]	Prospective	261[a]	Fore- und upper arm[a]	4.4 (n.d.)
18	Pistor 2003 [34]	Prospective	25	Elbow	n.d.
19	Poonai 2017 [35]	single-centre	169	Distal forearm	11 (3.3)

Table 4: Characteristics of the included diagnostic accuracy studies (multipage table)

	Study	Study design	Patient number N (analysed)	Fracture site	Child age in years Mean (SD)
20	Rabiner 2013 [36]	Prospective, multicentre	130	Elbow	7.5 (5.4)
21	Rowlands 2017 [37]	Prospective, single-centre	419	Forearm	9.3 (3.5)
22	Sinha 2011 [39]	Prospective, single-centre	17[a]	Forearm [a, f]	12.7 (7–14)[b]
23	Snelling 2021 [40-42]	Prospective, single-centre	204	Forearm	9.5 (n.d.)
24	Snelling 2022 [44]	Prospective cohort study	38	Distal forearm	9 (3.4)
25	Tandogan 2015 [45]	Prospective, single-centre	105	Forearm[g]	9.8 (3.9)[f, h]
26	Tokarski 2018 [46]	Prospective	100	Elbow	7.9 (5.1)
27	Varga 2021 [47]	Prospective	365	Elbow	n.d. (1–14)[b]
28	Williamson 2000 [48]	Prospective[i], single-centre	26	Forearm	8 (2–13)[b]

a. The study also included other fractures; the data refer only to the upper limbs.
b. Span.
c. The fractures affected the distal upper arm.
d. Distal part of the radius and ulna; no carpal bones.
e. Median
f. 20% of the fractures were allocated to the elbow. As this was a small study with n = 17, the study as a whole was only allocated to the forearm.
g. The fractures predominantly affected the distal forearm. Among the identified fractures (n = 57), 50 were distal radius fractures.
h. Data refer to boys (N = 67). The age of the girls (N = 38) was mean: 9.1 (SD): (3.2).
i. The study authors emphasized that the vote of the ethics committee was obtained, from which a prospective design can be concluded.

SD: standard deviation

A total of 28 studies were analysed for the assessment of ultrasound in suspected fractures of the long tubular bones of the upper limbs. A total of 3245 children were included in the studies, the median study size was 100 ([25% quartile; 75% quartile] ([Q1; Q3]): [46,5; 123]). The median fracture prevalence was 54.9% ([Q1; Q3]: [45.4%; 65.3%]). Data on fractures of the forearm were provided by 19 studies [17,18,20-23,27-31,33,35,37,39-42,44,45,48] with a total of 2129 children; the median study size was 103 ([Q1; Q3]: [42; 145]). The median fracture prevalence was 55.8% ([Q1; Q3]: [49.6%; 68.1%]). 7 of the 19 studies provided results exclusively (or predominantly: Tandogan 2015 [45]) on distal forearm fractures [20,27,29-31,35,44]; the 12 remaining studies included other forearm fracture sites or did not specify these further [17,18,21-23,28,33,37,39-42,45,48]. Data on fractures of the elbow were provided by 8 studies with a total of 947 children [19,24-26,34,36,46,47], the median study size was 89.5 ([Q1; Q3]: [71; 118]). The median fracture prevalence was 46.7% ([Q1; Q3]: [38.2%; 58.3%]). Supracondylar humeral fractures were categorized as elbow fractures, as was the practice of the corresponding study authors. Data on 168 children with suspected fractures of the upper arm were extracted from 3 studies (Akinmade 2019 [18], Moritz 2008

[33], Ackermann 2010 [16]) (see below for results). The Ackermann 2010 study [16] limited the study to the proximal upper arm.

In 4 studies in which only elbow fractures were considered (Eckert 2014a [25], Rabiner 2013 [36], Tokarski 2018 [46], and Varga 2021 [47]), results from follow-up examinations were taken into account for the reference standard - X-ray. The follow-up was sometimes performed for all patients (Eckert 2014a [25]) or only in those cases in which the X-ray as the initial diagnostic procedure showed negative findings (Rabiner 2013 [36] and Tokarski 2018 [46]) or in which the X-ray showed negative findings and / or the ultrasound showed positive findings (Varga 2021 [47]). Follow-up X-rays were either generally performed on all children at the time of follow-up or only in cases where a fracture was still suspected, e.g. due to new recordings of clinical symptoms (including telephone interviews). The initial X-ray was therefore not the sole reference test. Positive X-ray findings at the time of follow-up were also included in the results of these studies as positive findings of the reference test.

Figure 4 of the full report shows all the sensitivity and specificity results of the individual studies as well as the results of the meta-analyses for all 3 fracture sites.

4.3.2 Overview of the investigated outcomes of the diagnostic accuracy studies

Data from the 28 included diagnostic accuracy studies [16-31,33-37,39-42,44-48] were used for the benefit assessment. Sensitivity and specificity were assessed as a measure of diagnostic accuracy. In addition, the results reported in these studies on the pain observed in connection with the diagnostic procedure are presented, but not used for the assessment (see also Section 4.3.5.4 and Table 34 of the full report).

4.3.3 Assessment of the risk of bias of results of diagnostic accuracy studies

A high risk of bias was found in 4 of 28 analysed diagnostic accuracy studies (see Table 29 of the full report): In 1 study (Pistor 2013 [34]), the risk of bias of patient selection was assessed as unclear, as no information on inclusion and exclusion criteria was available. In 2 other studies (Ko 2019 and Moritz 2008 [31,33]), the risk of bias of the reference test was rated as high, as blinding to the index test was not ensured, and in 1 of the 2 studies (Ko 2019) and in 1 further study (Varga 2021), the risk of bias of patient selection was (also) rated as high, as inappropriate patient exclusions could not be excluded with certainty [33,47].

4.3.4 Assessment of the transferability of the results of diagnostic accuracy studies

In 1 [34] of 28 analysed diagnostic accuracy studies, there were strong concerns about the transferability of the results, as this aspect was considered to be unclear with regard to patient selection due to missing information on inclusion and exclusion criteria (see Table 30 of the full report).

4.3.5 Results of diagnostic accuracy studies

4.3.5.1 Results on the outcome "sensitivity of fracture ultrasound"

Based on all available data, the bivariate meta-analysis yields a sensitivity estimate of 96.6% (95% CI: [94.3%; 97.9%]) (see Table 31 of the full report). Overall, the bivariate meta-analysis shows little heterogeneity based on the 95% confidence and 95% prediction regions (see Figure 5 of the full report). Only 1 study (Pistor 2003 [38]) deviated significantly from the other studies in terms of both sensitivity and specificity (see Figure 4 of the full report).

4.3.5.2 Subgroup and sensitivity analyses

The planned (subgroup) analyses with regard to sex and age were not possible as the presentation of results in the studies did not provide the necessary data.

Further subgroup analyses could not be carried out because the available data were insufficient in the subgroup combinations. Sensitivity analyses were carried out instead.

Categorization of the studies according to fracture site

As can be seen from the description of the study characteristics of the 28 test accuracy studies in Section 4.3.1, it is not possible to divide the arms into 3 strictly separate fracture sites (distal forearm, elbow and proximal upper arm) due to the overlaps in the studies on the definitions of the fracture sites. Therefore, for the sensitivity analyses, the following 3 mixed categories or fracture sites were defined: forearm, elbow and upper arm.

Sensitivity analyses regarding fracture site, risk of bias and follow-up X-rays for the outcome of sensitivity

Sensitivity analyses were performed for the outcome of sensitivity with regard to fracture site ([distal] forearm, elbow, upper arm), risk of bias (low versus high) and consideration of follow-up data (no versus yes).

With regard to these 3 aspects, it was checked whether the result was called into question based on all available data. For this purpose, models without and with the respective factor were compared using the likelihood ratio test (LRT) to check whether the respective factor has an influence on the result.

The bivariate meta-analysis of 19 studies (2129 children) on fractures of the forearm resulted in a sensitivity estimate of 96.9% (95% CI: [93.9%; 98.5%]), see Figure 6 and Figure 7 of the full report. With regard to elbow fractures, based on 8 studies (947 children) the sensitivity estimate is 97.4% (95% CI: [89.1%; 99.4%]), see Figure 8 and Figure 9 of the full report, and is thus consistent with the overall result for all fractures, even though the lower limit of the 95% CI is just below the 90% limit. The univariate meta-analysis of 3 studies (168 children) on fractures of the upper arm results in a sensitivity estimate of 93.5% (95% CI: [72.3%; 99.7%])

(see Figure 10 of the full report). One of the 3 studies on the upper arm (Akinmade 2019) shows an overall estimate of sensitivity of only 84.6%. However, the discussion in [23] of the corresponding analysis, which was based on only 39 people, indicated that the only two false-negative cases affected the distal upper arm, i.e. the elbow. The sensitivity for the non-distal upper arm was therefore 100% in this study. However, due to the lower number of cases, the result for the fracture site of the upper arm has a significantly wider CI than the analyses for the other two fracture sites. At 72.3%, the lower limit of the 95% CI is below the pre-specified limit. It therefore remains unclear whether the required sensitivity of 90% is achieved when analysing solely the studies on the upper arm.

The comparison of studies with a low risk of bias versus studies with a high risk of bias (sensitivity: 96.1%; 95% CI: [93.7%; 97.6%] vs. sensitivity: 98.9%; 95% CI: [64.6%; 100.0%]) and of studies without follow-up data for the reference standard versus studies with follow-up data (sensitivity: 96.2%; 95% CI: [93.7%; 97.8%] vs. sensitivity: 97.7%; 95% CI: [82.6%; 100.0%]), showed similar results to each other and to the overall results (see Table 31 of the full report).

The exclusion of studies with a high risk of bias or studies that included results from follow-up X-rays does not call into question the results of the overall data. The subsequent sensitivity results are comparable (see Table 31 of the full report).

To investigate the possible influence of fracture site (forearm, elbow, upper arm), risk of bias (low, high), and inclusion of follow-up X-rays (yes, no), LRTs were performed in which the bivariate model without these factors is compared with the respective model with the factor as an explanatory variable. The tests are not statistically significant (fracture site: pLRT = 0.133; risk of bias: pLRT = 0.750; follow-up data: pLRT = 0.349; see Table 31 of the full report).

4.3.5.3 Results on the outcome “specificity of fracture ultrasound”

To demonstrate the benefit of ultrasound, it is sufficient to consider sensitivity, but specificity should also be within an acceptable range to ensure that a sufficiently large proportion of children benefit from ultrasound.

The estimate for specificity in the bivariate meta-analysis across all fracture sites was 92.7%; the corresponding 95% CI was [87.9%; 95.7%] (see Table 31 of the full report). Measured by the size of the 95% CI, the result is more heterogeneous than the result for sensitivity. However, it indicates sufficiently high specificity to draw a conclusion on benefit based on sensitivity.

Sensitivity analyses with regard to fracture site, risk of bias and follow-up X-rays for the outcome of specificity

Sensitivity analyses were also performed for the outcome of specificity with regard to the 3 aspects:

- fracture site (forearm, elbow, upper arm)
- risk of bias (low versus high), and
- consideration of follow-up data (no versus yes)

The greater heterogeneity of the results for specificity can be seen in the sensitivity analyses with regard to fracture site (Figures 8-10 of the full report), risk of bias and follow-up data. Specificity differs from the overall result in the studies on elbow fractures (specificity: 84.7%; 95% CI: [71.2%; 92.6%]), in the studies with a high risk of bias (specificity: 90.1%: 95% CI: [61.3%; 99.9%]) and in the studies that include follow-up X-ray data (specificity: 83.8%; 95% CI: [63.9%; 96.2%]). The results in these groups are recognizably lower compared to the overall result. However, the corresponding analyses for effect modification, based on the LRTs, are not statistically significant (see previous Section 4.3.5.2).

4.3.5.4 Supplementary presentation of results from individual studies on pain associated with the diagnostic procedure

In 7 of the 28 included diagnostic cohort studies [16,18,20,27,35,37,40], data on the outcome of pain associated with the diagnostic procedure were reported. 3 of these studies [20,27,35] reported a statistically significant benefit of ultrasound versus X-ray with regard to pain experienced in connection with the diagnostic procedure. The 4 remaining studies did not show an advantage of one form of diagnostic procedure over the other (see Table 36 of the full report for the reported results). As these results are not data from RCTs and as the diagnostic cohort studies did not randomize the order in which ultrasound and X-ray were performed, these data cannot be used for the benefit assessment, as the certainty of results in the intra-individual comparison is too low.

4.3.6 Summary assessment of the results of the diagnostic accuracy studies

Usable data from 28 prospective cohort studies on test accuracy were available. With an estimate of 96.6% (95% CI: [94.3%; 97.9%]), the sensitivity result from these studies is well above the required minimum level of 90%. The results for sensitivity are homogeneous across all fracture sites and independent of the risk of bias and whether the X-ray result was based on images taken at the times of follow-up diagnostics. However, the result for the fracture site “upper arm” shows a markedly wider CI due to the lower number of cases.

Assessment of the extent of unpublished data

As non-randomized studies do not have to be registered in a study registry at the start of the study, publication bias can only be assessed to a very limited extent. Of the diagnostic cohort studies without reported test accuracy results, for 2 studies on relevant fracture sites, the planned end of study date was more than 12 months before the date of the registry check (see Table 12 of the full report). The planned sample size in these 2 studies was approximately 5% of the total sample size in all studies, so that a distortion of the results due to publication bias appears less likely.

Weighing of benefits and harms

In the present research question, the evaluation of the sensitivity of ultrasound versus X-ray is sufficient for deriving a conclusion on benefit, because ultrasound does not influence the type of fracture treatment (if a fracture is detected). Even if the implementation of the index test varied, including the use of different devices and with a very heterogeneous group of examiners in terms of expertise, the results on sensitivity are largely homogeneous. The sensitivity analyses, e.g. with regard to fracture site (forearm or elbow or upper arm), also show comparable results for the point estimates. The sensitivity of ultrasound is above 90% with sufficient certainty and is therefore sufficiently high.

Ultrasound has an inherent methodological advantage over radiography in that there is no exposure to ionizing radiation. Approximately half of children with a suspected fracture do not have a fracture; a sonographic diagnosis of "no fracture" means that unnecessary radiation exposure can be avoided in these children. The high sensitivity ensures that only an acceptably small proportion of the children examined will receive a false-negative result. Specificity is within an acceptable range, which ensures that a large proportion of children are correctly diagnosed as not having a fracture and therefore do not need to be X-rayed.

Due to the mechanism of action, it can be assumed that ultrasound for fracture diagnosis has no harmful effects. This applies to both direct and indirect (i.e. treatment-related) effects. This is because ultrasound generally has no influence on the type of treatment if a fracture is detected (with or without subsequent radiological confirmation). Even the slightly later start of treatment by the first sonographic and then the radiological diagnosis in children with fractures is not expected to have any relevant consequences.

Supplementary results from the test accuracy studies on pain associated with the diagnostic procedure do not suggest that fracture ultrasound is more painful than X-ray; on the contrary, in 3 of the 7 studies, the results tend to indicate that fracture ultrasound is less painful than X-ray - however, the certainty of the results is too low, meaning that these results cannot be used to derive a benefit.

The concerns regarding the transferability of the results from the studies were minor, with the exception of 1 study. The proportion of unpublished results from 2 studies is low at approx. 5% of the total number of cases for all fracture sites, so that there is no restriction of the certainty of the results.

Overall, the data provide an indication a greater benefit of ultrasound versus X-ray in the diagnosis of fractures for the fracture site of the forearm and elbow. Due to the limited evidence on the fracture site of the upper arm, which is based on only 168 people, only a hint of a benefit of ultrasound versus X-ray could be derived for the site of the non-distal upper arm.

4.4 Summary assessment for both study types

Overall, the assessment of the results of the BUCKLED RCT as a study on the diagnostic-therapeutic chain for the fracture site "distal forearm" provided an indication of a greater benefit of ultrasound versus X-ray, based on the outcome of radiation exposure. The results for the other outcomes did not contradict this finding. Since the assessment of the results from the diagnostic accuracy studies also showed an indication of a greater benefit of ultrasound versus X-ray for the fracture site "(distal) forearm", overall, proof of a greater benefit of ultrasound versus X-ray is derived due to the resulting higher certainty of conclusions for this fracture site.

For the fracture site "elbow", the results of the diagnostic accuracy studies provide an indication of a greater benefit of ultrasound versus X-ray. For the fracture site "upper arm", however, only a hint of a greater benefit of ultrasound versus X-ray is derived due to an evidence base of only 168 people.

The following Table 5 summarizes the conclusions on the (greater or lesser) benefit or harm across all study designs.

Table 5: Overall conclusions on the (greater or lesser) benefit or harm in studies on the diagnostic-therapeutic chain and diagnostic accuracy depending on fracture site

Fracture site	Studies on the diagnostic-therapeutic chain	Diagnostic accuracy studies	Overall conclusion on (greater or lesser) benefit or harm
Forearm	⇑[a]	⇑	⇑⇑[a]
Elbow	–	⇑	⇑
Upper arm	–	⇗	⇗

⇑⇑: Proof of a greater benefit of ultrasound versus X-ray.
⇑: Indication of a greater benefit of ultrasound versus X-ray.
⇗: Hint of a greater benefit of ultrasound versus X-ray.
–: No data available.
a. Assessment refers to the distal forearm

4.5 Key points of a testing study

As the corresponding benefit assessment is only based on data from 168 people, a confirmatory study should be considered for the fracture site “non-distal upper arm”. Since diagnostic cohort studies are currently not regularly registered prospectively in a study registry, it is not possible to estimate whether and when further suitable evidence will be added to confirm the previous study results on fracture ultrasound for non-distal upper arm fractures. Therefore, the key points of a possible testing study are outlined below.

Study type

A diagnostic cohort study should be carried out in which fracture ultrasound as an index test is compared with X-ray as a reference standard. As already explained above, it is expedient and sufficient in the present research question to demonstrate by means of sufficiently high sensitivity that the negative ultrasound findings “no fracture” only contains a small proportion of children with overlooked fractures and that ultrasound is therefore suitable for avoiding X-rays (and the associated disadvantages). A minimum specificity should be defined (e.g. based on the results from this report) so that the study objective of minimum sensitivity is not achieved at the expense of specificity.

Target population

Children with a suspected fracture of the proximal or middle third of the upper arm are to be examined in the study. Children in whom a fracture is already recognizable on the basis of the findings of the clinical examination (e.g. axial deviation) are to be excluded. Further reasons for exclusion (e.g. underlying bone disease, polytrauma, etc.) must be defined as part of the study protocol.

Test and control intervention(s)

Fracture ultrasound as an index test is the first diagnostic modality for all study participants. Adequately trained staff should perform the ultrasound in a standardized form. Secondly, all study participants receive an X-ray for fracture diagnosis in accordance with medical standards. The sonographic index test and the radiological reference test are to be mutually blinded, i.e. they are to be performed and evaluated in ignorance of the results of the other test. The subsequent treatment depends on the radiological findings. In the case of discordant findings, a short-term follow-up can be carried out using the clinically indicated follow-up diagnostic procedures to check the reasons for the deviations in the findings and what the therapeutic consequences would have been. However, the initial X-ray for fracture diagnosis is the sole reference standard.

Study planning

The aim of the study is to prove that an unremarkable sonographic finding can predict an unremarkable (i.e. negative) radiological finding with sufficient accuracy. Sensitivity is

therefore crucial for the study hypothesis, because with sufficiently high sensitivity (i.e. a low proportion of false-negative findings), many children could in future be spared the need for X-rays to diagnose fractures and the associated radiation exposure, which would be a benefit.

The available studies - both on non-distal humeral fractures and on elbow and forearm fractures - suggest that sensitivity is around 96%. Furthermore, as explained in Section A2.4.3.2 of the full report, the threshold should be that sensitivity is safely above 90%. Accordingly, in the statistical sense a testing study aims to demonstrate a lower limit of the 95% CI of greater than 90% for sensitivity.

Taking into account the incidence of humeral fractures and the studies conducted to date, a sample size of 200 to 500 children is a realistic size for the planned testing study. With a fracture prevalence in the study population of around 50% and an assumed sensitivity of ultrasound of a good 95%, a sample size of 200 to 500 children would be sufficient to demonstrate a sensitivity of more than 90% (taking into account the existing evidence) in accordance with the usual statistical specifications (90% power). These comments on sample size estimation are not to be understood as a binding calculation, but as an approximate estimate of the required sample size. An exact calculation of the sample size must be made as part of the actual study protocol. The recruitment target should not be determined by the total number of participants, but by the number of children with fractures, in order to safeguard against a deviating fracture prevalence.

The suspected fracture site should be taken into account in the planning and analysis of the study in the form of subgroup analyses planned a priori.

Recruitment must be multicentre and can cover both the inpatient and the outpatient sector. Overall, the duration of the testing study (from the start of work on the study protocol to the final study report) can be expected to be around 2 to 3 years.

During study preparation, it should be checked whether notification of the study to the competent higher German federal authority can be waived in accordance with § 47 of the Medical Device Law Implementation Act (MPDG) because no additional invasive or stressful procedures will be carried out as part of the study. The study must be conducted in compliance with the rules of Good Clinical Practice.

Study costs

For studies with a medium sample size (here 200 to approx. 500 patients) and very low expenditure (test accuracy study), a study-specific expenditure of around €1000 per participant can be estimated. Based on these assumptions, estimated study costs of €200,000 to € 500,000 can be expected. This estimate corresponds to the fact that many of the primary studies used in this report were obviously conducted without external funding.

The cost estimate figures are for guidance only and are not suitable as a basis for contractual cost agreements.

Prospects of success of a testing study

The Ackermann 2010 study shows that diagnostic test accuracy studies on ultrasound for the diagnosis of fractures can be carried out in Germany without any recognizable problems. The patient population is easily identifiable and sufficiently large. The inability of many children suitable for the study to give informed consent is also not a relevant problem. The acceptance of additional sonographic diagnostic procedures as part of the study is considered to be good from the point of view of the children and their parents, as they can be carried out quickly and with little pain. Safety concerns are also unlikely to play a major role, as no further study-specific interventions are carried out in addition to fracture ultrasound and the guideline-compliant treatment is not affected. As the recruitment of suitable clinical study centres also appears to be unproblematic (see also the comments on the preliminary report in Table 37 of the full report), it can be assumed that recruitment will be rapid overall. A testing study that is suitable for gaining the necessary knowledge for assessing the benefit of the procedure is therefore easily realizable.

It seems quite possible that the evidence gap for non-distal upper arm fractures will be closed in the next few years, even without a testing study. This is because the relatively large number of primary studies suggests that further studies will be published in the future, some of which will probably also deal with fractures of the proximal or middle third of the upper arm. However, due to the lack of mandatory registration of non-randomized studies, it is not possible to identify currently ongoing studies. Nevertheless, it seems reasonable as an alternative to forego a testing study and await further generation of international evidence.

5 Classification of the assessment result

According to Körner 2020 [3], there were 27,239 fractures of the upper limbs in children aged 0 to 14 years in Germany in 2017. In the included studies, 45.1% of the recruited suspected cases of fractures of the long tubular bones of the upper limbs were fracture-negative patients in the reference diagnostic test. If this estimate is extrapolated using the estimated specificity of 92.7% and the occurrence of such fractures in children aged 0 to 14 years in Germany, which Körner 2020 - as mentioned above - puts at 27,239 cases for 2017, around 20,700 children could have been spared an X-ray of their (actually non-fractured) arm. On the other hand, based on the estimated sensitivity of 96.6%, around 930 false-negative ultrasound results could be expected. This means that approx. 930 children with a fracture would initially remain unrecognized and therefore untreated. However, experience has shown that affected children usually return to the doctor within a short time due to persistent pain, so that subsequent harm due to delayed treatment is generally unlikely. In this context, it should be noted that the fractures not initially recognized by ultrasound are more likely to be fractures of a simpler

type, such as non-displaced fractures, so that subsequent harm due to vascular or nerve lesions is very unlikely anyway. In addition, if the bruising is severe, the arm may also be immobilized. In the overall assessment, it can be estimated on the basis of the above figures that for every 22 children who are spared an X-ray, there is on average around 1 child in whom a fracture is initially overlooked.

According to the S2e guideline "Ultrasound for fracture diagnosis" from 2023 [55], ultrasound should be used as the standard diagnostic procedure for suspected distal forearm fractures in children up to 12 years of age (recommendation grade A / evidence level 2++). X-ray monitoring is not necessary for conservative treatment and should only be added if surgical treatment is planned. Furthermore, according to the S2e guideline, ultrasound serves as the first diagnostic procedure for the detection of an elbow fracture in children up to 12 years of age (recommendation grade A / evidence level 2++) [55]. This provides the medical indication for a mandatory X-ray. If the findings are unremarkable, a wait-and-see approach can be adopted and, in the event of persistent pain after 5 days, an X-ray can be performed. The S1 guideline "Trauma of the musculoskeletal system in childhood and adolescence - Imaging diagnostics" from 2019 [9] also states that ultrasound may be sufficient for diagnosing a possible forearm fracture that does not require surgical treatment. The S1 guideline on "Forearm shaft fracture in childhood" [4] from 2016 is currently being revised. Overall, the report results and guideline recommendations for forearm fractures and elbow fractures are largely the same.

If a proximal humeral fracture is suspected, the S2e guideline "Ultrasound for fracture diagnosis" [55] recommends ultrasound as the initial diagnostic procedure in children up to 12 years of age with recommendation grade B (evidence level 2). The guideline group explains that only 4 observational studies with a low number of cases are available to date for this fracture site. The recommendation grade of the guideline reflects limited certainty and is correspondingly lower: 3 of these 4 studies were excluded from the present assessment: 1 study did not include any children [56], the second study is a mathematical modelling of X-ray of the upper arm [57] and the third study [58] investigates ultrasound-based treatment guidance and as a result only evaluates data on children with a positive fracture diagnosis, so that it is not possible to create a 2x2 table from the published results. The fourth study cited in the guideline (Ackermann 2010 [16]) was used for the present assessment. However, it only includes 33 children and has limited informative value due to the low number of cases.

The S1 guideline "Trauma of the musculoskeletal system in childhood and adolescence - Imaging diagnostics" from 2019 [9] describes that subcapital humeral fractures can be reliably ruled out by ultrasound. However, if a fracture is detected, an X-ray should be performed to rule out a pathological fracture. Furthermore, the S1 guideline on "Proximal humeral fracture in children" from 2021 [59] states that ultrasound is used to rule out fractures or as an

additional examination for reliable axis assessment. However, there is no recommendation grade for this and reference is made to only 1 study [10], which was not used in the present assessment because it did not address the research question.

As part of the derivation of the evidence map for this benefit assessment, two further studies were analysed for the fracture site "upper arm" (Akinmade 2019 [18] and Moritz 2008 [33]). These studies support the derived hint of a greater benefit of ultrasound versus X-ray in the diagnosis of fractures. There are now 3 analysed studies (Ackermann 2010 [16], Akinmade 2019 [18], Moritz 2008 [33]) with a total of 168 children with a suspected fracture of the upper arm, which expand the available evidence on fractures of the upper arm.

A meeting of affected parents took place during the preparation of the report. Parents reported long waiting times at the hospital as well as stress for the child. Hope was expressed that ultrasound might be associated with less waiting time and/or that an outpatient specialist could carry it out. Ideally, a paediatrician would perform the ultrasound, as the child would be in a familiar environment there. The parents also stated that a false-negative finding is not considered to be dramatic, as a new visit to the doctor would take place promptly if the pain persists.

In the included diagnostic accuracy studies, the experience of the examiners with regard to using ultrasound for fracture diagnosis varied greatly. There are studies [17,27,29,30,39,40,45] in which the examiners received an introduction to ultrasound for the first time. In contrast, there are studies [18,20,21,26,31,33,35,44,48] with examiners who have years of experience, have completed longer training courses or are described as experts in ultrasound. However, even within the studies, the experience of the examiners is sometimes described as very heterogeneous [16,25,28,36,37,46,47]. Some further studies do not provide any information regarding experience with fracture ultrasound [19,22-24,34]. Overall, however, all studies show homogeneous results with regard to sensitivity, regardless of the experience of the examiners. In this context, the S2e guideline on fracture ultrasound [55] states that appropriate expertise and practical experience must first be acquired as a prerequisite for the use of ultrasound. Like in some test accuracy studies, ultrasound was performed in the BUCKLED RCT by non-physicians such as nurse practitioners and other health care professionals.

In the current health care context, an X-ray is the standard diagnostic procedure for suspected fractures. It was therefore used as the reference standard in this report. In this context, however, it should be noted that X-ray as a reference standard does not represent a gold standard. This must be taken into account when interpreting the data. For example, the reported results on elbow fractures in 4 studies [25,36,46,47] showed that X-ray also produced incorrect results in some cases. In particular, fractures that were most likely to be in the area of soft tissue injuries and/or were otherwise unfavourably located for X-ray diagnosis ("fat

pad sign") were missed [36,46]. It also happened that the fracture-positive findings of the X-ray as the initial diagnostic procedure were not confirmed [25]. Other studies have also reported some incorrect X-ray results [17,18,21,24].

6 Conclusion

A total of 28 test accuracy studies on ultrasound and 1 RCT on the diagnostic-therapeutic chain were assessed. The meta-analysis of these 28 studies showed that overall, the sensitivity of ultrasound was safely above the required minimum level of 90% for all relevant fracture sites (forearm, elbow and upper arm). Sensitivity analyses considering these 3 fracture sites each showed a similar result for sensitivity.

In children with a suspected distal forearm fracture, the RCT confirmed that ultrasound reduces radiation exposure (indication of greater benefit), has no functional disadvantages (hint of non-inferiority), and also shows comparable results for other morbidity outcomes. Therefore, the overall assessment of test accuracy and patient-relevant outcomes in children with a suspected distal forearm fracture provides proof of a greater benefit of ultrasound versus X-ray.

In children with a suspected elbow fracture, overall, there is an indication of a greater benefit on the basis of the test accuracy studies.

In children with a suspected fracture of the upper arm, overall, there is only a hint of a greater benefit. This is due to an evidence base of only 168 people, combined with an imprecise sensitivity estimate (lower limit of the 95% CI: about 72%). Due to the weaker evidence underlying the benefit assessment, a confirmatory cohort study should be considered for the fracture site "non-distal upper arm". Therefore, the key points of a potential testing study were outlined for this fracture site.

References for English extract

Please see full final report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects/d22-02.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to December 06, 2022

The following filter was adopted:

- Systematic review: Wong [60] – High specificity strategy

#	Searches
1	exp Ultraultrasound/
2	(sonograph* or ultraso*).ti,ab.
3	or/1-2
4	exp Fractures, Bone/
5	fractur*.ti,ab.
6	or/4-5
7	Cochrane database of systematic reviews.jn.
8	(search or MEDLINE or systematic review).tw.
9	meta analysis.pt.
10	or/7-9
11	10 not (exp animals/ not humans.sh.)
12	and/3,6,11
13	12 and (english or german or multilingual or undetermined).lg.
14	..l/ 13 yr=2012-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Ultraultrasound"[mhe]
2	sonograph* OR ultraso*
3	#2 OR #1
4	"Fractures, Bone"[mhe]
5	fractur*
6	#5 OR #4
7	#6 AND #3
8	(*) FROM 2012 TO 2022
9	#8 AND #7

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to July 10, 2023

#	Searches
1	exp Ultraultrasound/
2	(sonograph* or ultrasonograph* or ultrasound*).ti,ab.
3	or/1-2
4	exp Fractures, Bone/
5	fractur*.ti,ab.
6	or/4-5
7	exp Arm Injuries/
8	((upper extremit* or arm* or forearm* or ulna* or humeral* or humerus* or elbow or radius* or long bone*) adj9 (fractur* or trauma*)).ti,ab.
9	or/7-8
10	exp pediatrics/
11	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
12	(school child or school child* or school or school*).ti,ab.
13	or/10-12
14	and/3,6,9,13
15	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
16	hi.fs. or case report.mp.
17	or/15-16
18	14 not 17
19	18 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2023 July 10

#	Searches
1	exp echography/
2	(sonograph* or ultrasonograph* or ultrasound*).ti,ab.
3	or/1-2
4	exp fracture/
5	fractur*.ti,ab.
6	or/4-5
7	exp arm fracture/
8	((upper extremit* or arm* or forearm* or ulna* or humeral* or humerus* or elbow or radius* or long bone*) adj9 (fractur* or trauma*)).ti,ab.
9	or/7-8
10	exp child/
11	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).af.
12	(school child or school child* or school or school*).ti,ab.
13	or/10-12
14	and/3,6,9,13
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not (Conference Abstract or Conference Review or Editorial).pt.
18	17 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 7 of 12, July 2023

#	Searches
#1	[mh "Ultraultrasound"]
#2	(sonograph* or ultrasonograph* or ultrasound*):ti,ab
#3	#1 or #2
#4	[mh "Fractures, Bone"]
#5	fractur*:ti,ab
#6	#4 or #5
#7	[mh "Arm Injuries"]
#8	((upper extremit* or arm* or forearm* or ulna* or humeral* or humerus* or elbow or radius* or long bone*) NEAR/9 (fractur* or trauma*)):ti,ab
#9	#7 or #8
#10	[mh "pediatrics"]
#11	(infan* or newborn* or new-born or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*)
#12	(school child or school child* or school or school*):ti,ab
#13	#10 or #11 or #12
#14	#3 and #6 and #9 and #13
#15	#14 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#16	#15 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)))
#17	#16 in Trials

A.2 Searches in study registries

ClinicalTrials.gov

Provider: U.S. National Institutes of Health

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

Search strategy
AREA[ConditionSearch] fracture AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child" AND ultrasound

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

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

Search strategy
(fracture OR fractures) AND (ultraultrasound OR ultrasound) // Search for clinical trials in children