Penile traction therapy for induratio penis plastica[1]

EXTRACT

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This report was prepared in collaboration with external experts.

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

Patient and family involvement

One patient or family member was consulted during the preparation of the report. The aim of the discussion was to obtain information on the following topics: The impact of the condition on life and daily activities and how he or she copes, treatment preferences including treatment goals, and experiences and concerns about treatment.

IQWiG would like to thank the participant for taking part in the discussion. He or she was not involved in the actual writing of the report.

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Penile Induration, Traction, Benefit Assessment, Systematic Review

Key statement

Research question

The objective of this investigation is to

- assess the benefit of treatment with penile traction therapy compared to treatment with other therapies available in Germany or no treatment

in people with induration penis plastica (IPP) with regard to patient-relevant outcomes.

Conclusion

Two randomized controlled trials were included to answer the research question. Both studies compared penile traction therapy versus no treatment.

With regard to the outcome of penile deformation, the data showed that. in the short term, i.e. immediately after the 3-month treatment, traction therapy reduced the curvature of the penis caused by the disease more than no treatment. However, no usable data were available on whether this effect persists in the longer term, and no hint of benefit was derived.

No advantages were found for the outcomes of pain, sexual function, and symptom burden; this resulted in no hint of benefit of traction therapy compared to no treatment.

No data are available for the outcomes of mental health problems or health-related quality of life.

With regard to the outcome of side effects, no hint of harm from traction therapy compared to no treatment was derived on the basis of the available data.

In summary, no hint was derived for a benefit or harm from traction therapy compared to no treatment.

Based on the available results on the reduction of penile curvature at the end of the 3-month treatment phase, it can be concluded that traction therapy is a necessary alternative treatment for IPP compared to no treatment. As no ongoing studies were identified which would be fundamentally suitable for demonstrating a benefit, key characteristics for a possible testing study were outlined.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CCH	collagenase clostridium histolyticum
EAU	European Association of Urology
ED	erectile dysfunction
GAPD	Global Assessment of Peyronie's Disease
IFN	interferon
IIEF	International Index of Erectile Function
IPP	induratio penis plastica
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MD	mean difference
OR	odds ratio
PDQ	Peyronie's Disease Questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
SR	systematic review

1 Background

Induratio penis plastica (IPP) or Peyronie disease is a benign, acquired disease of the tunica albuginea (the layer of connective tissue which surrounds the corpora cavernosa of the penis). This leads to plaque formation, which causes the tissue to lose elasticity and the penis to become deformed and typically bent, especially when erect. Plaques consist mainly of collagen-containing connective tissue and may calcify. The exact aetiology of the disease is unknown. The main cause is thought to be repeated microtrauma, which may occur during sexual intercourse, for instance, and lead to localized excessive scarring via inflammatory processes [1]. A genetic predisposition appears increasingly likely in the pathogenesis, although these findings do not yet have any diagnostic or prognostic applications and do not currently play a role in the selection of treatment options [2].

The disease progresses in 2 phases, which are delineated as follows [1,3-5]:

- In the **acute phase** (inflammatory, active phase), there is often pain in the shaft of the penis, which mainly manifests itself when the penis is erect. This leads to gradual plaque formation and successive deformation of the penis. Current literature shows that the duration of the acute phase varies greatly and is estimated to be between 3 and 18 months.
- The **stable phase** (post-inflammatory, chronic phase) is reached when the inflammatory reaction has subsided and plaque formation has stabilized. Pain is less frequent in this phase, and deformation of the penis no longer progresses.

The scar tissue usually forms dorsally (on the upper side of the penis), which leads to an upward curvature during an erection (dorsal deviation) [6]. More rarely, the underside of the penis (ventral plaque formation) or one of the sides (lateral plaque formation) is affected, resulting in downward or lateral curvature. In case of scarring of the inner, circular fibres of the tunica albuginea, a dent or hourglass-shaped constriction may form [3,4]. Plaques can lead to a shortening of the overall length of the penis (with or without deviation) [6]. The deformation of the penis usually remains [6]. Studies reported spontaneous regression of the curvature in 3% to 13% of men [7].

In the past, the prevalence of IPP was probably underestimated [4]. Depending on factors such as age group, comorbidities, and survey method, prevalence rates of 0.4% to 20.3% are reported, with a higher prevalence in patients with erectile dysfunction (ED) or diabetes [7]. Study results suggest that the disease is underdiagnosed [8,9]. Prevalence increases with age. The average age of onset is between the ages of 50 and 60 [6].

IPP can significantly affect sexual function and mental health [10]. About one-third of affected men report suffering from ED [6]. An increased rate of anxiety disorders and depression is also

reported [11]. Possible causes include concerns about appearance, impairment of body image, self-confidence, and identity as well as sexual dysfunction, fear of sexual failure, and fear of stigmatization [12]. Penetrative sexual intercourse can become hampered or impossible and painful for sexual partners [13]. Many of those affected report relationship problems [10].

There is currently insufficient evidence regarding effective drug treatments aimed at halting the progression of the disease in the acute phase. Due to a lack of effectiveness or lack of evidence, oral pharmaceuticals such as L-carnitine, tamoxifen, vitamin E, and potassium 4-aminobenzoate, which is authorized in Germany for the treatment of IPP, are not recommended by the European Association of Urology (EAU) guideline. Treatments in the acute phase are therefore aimed in particular at alleviating pain. According to the EAU guideline, non-steroidal anti-inflammatory drugs (NSAIDs) can be used for this purpose. The EAU guideline also mentions phosphodiesterase (PDE)-5 inhibitors for treatment in the active phase. According to the EAU guideline, extracorporeal shock wave therapy (ESWT) can also be used as an option to reduce pain [7].

Treatment in the stable phase is intended to correct the curvature and enable penetrative sexual intercourse. The EAU guideline mentions intralesional injections with interferon-alpha (IFN-α) or collagenase clostridium histolyticum (CCH) as potential conservative treatments. However, intralesional therapies are rarely used in Germany: IFN-α is not authorized for this therapeutic indication [3], and CCH has not been marketed in Europe since 2020 [14].

In the absence of available and demonstrably effective conservative therapies for IPP, surgical therapies play a relevant role in reducing penile curvature and restoring sexual function. The prerequisite for surgery is that the IPP has been in the stable phase for at least 3 months, and sexual function is impaired. The choice of surgical technique depends on penis length, degree of curvature, and erectile function [7]. Provided there is adequate erectile function, 2 types of surgical procedures are possible: (1) surgical procedures to shorten the tunica by means of plication or reduction stitches to the convex side. This surgical technique is recommended if the penis is not complexly deformed and if a loss of penis length due to the operation is acceptable for the person concerned. (2) If the penis is either no longer long enough for plication, is curved > 60 degrees, or has complex deformities, a tunica lengthening approach using an incision or partial excision of the plaque, combined with a graft, is recommended. However, this procedure is associated with a higher risk of complications with regard to other penile (functional) disorders such as postoperative ED and numbness of the glans [7]. In patients who suffer from IPP as well as severe ED resistant to drug treatment, implantation of a penile prosthesis is recommended, possibly supplemented by surgical straightening of the penile shaft [3,7].

Penile traction therapy is a conservative treatment option in which the penis is mechanically stretched using controlled traction [15]. Bar expander systems are primarily used for this

purpose. The mechanical stretching should lead to remodelling of the connective tissue via various cellular processes (cellular mechanotransduction) and thus reduce the curvature. The systems used for traction therapy sometimes differ significantly in terms of their design as well as application aspects such as wearing time [16]. Traction therapy can be used both as monotherapy and as part of a multimodal treatment approach, regardless of the stage of the disease [7].

2 Research question

The objective of this investigation is to

- assess the benefit of treatment with penile traction therapy compared to treatment with other therapies available in Germany or no treatment

in people with IPP with regard to patient-relevant outcomes.

3 Methods

The target population of the benefit assessment consisted of people with IPP requiring treatment. The experimental intervention was penile traction therapy alone or as part of multimodal treatment. Other therapies available in the German healthcare context or no (active) treatment was used as comparator interventions.

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

- Morbidity (e.g. penile deformation, pain, sexual function, mental health problems)
- Health-related quality of life
- Side effects

In addition to the overarching outcome of penile deformation, data on the outcome of penile shortening, operationalized as mean stretched penis length, were presented. On this basis alone, however, no (greater) benefit was found.

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

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

It was ascertained whether at least 1 high-quality, current systematic review (SR) existed whose information retrieval was a suitable basis (hereinafter: basic SR).

If that was the case, a second step followed, where a supplementary search was conducted for studies for the time period not covered by the basic SR(s). Otherwise, the search for studies was carried out without time restriction.

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

In addition, the following information sources and search techniques were taken into account: study registries, manufacturer queries, documents transmitted by the Federal Joint Committee (G-BA), the screening of reference lists, documents made available from hearing procedures, and author queries.

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 the risk of bias were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described in the order of outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

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.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

In cases where there is 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.

4 Results

4.1 Results of the information retrieval

No systematic reviews were taken into account as basic SRs for the purpose of identifying primary studies.

The information retrieval resulted in 2 RCTs relevant for the research question. No planned or ongoing studies were identified.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 29 June 2023.

Table 1: Study pool of the benefit assessment

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / Result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Moncada 2019	Yes [17]	No	No	No
Ziegelmann 2019	Yes [18,19]	Yes [20] / yes [20]	No	No

4.2 Characteristics of the studies included in the assessment

In the Moncada 2019 study [17], a total of 93 people were recruited at 6 university hospitals in Spain between March 2016 and June 2017 and randomized at a 1:1 ratio. All participants had stable IPP, defined in this study as a disease duration of at least 12 months. The average age at baseline was around 58 years, and the average degree of curvature was around 70 degrees (range: 58 to 105 degrees), which is deemed a severe curvature [21,22]. Individuals with ED, hourglass phenomenon, indentation of the tunica albuginea and/or multiplanar curvature were excluded, as were individuals with previous intralesional treatments. The intervention group was treated with traction therapy, while the control group received no treatment. In the intervention arm, a rod expander was used to stretch the penis in a straight direction. During an initial 10-day adaptation phase, the daily wearing time was increased from 3 to up to 6 hours. After that, the daily target wearing time was 6 to 8 hours. Patients were instructed to take off the traction device for 30 minutes every 2 hours. The traction device was to be used for 12 weeks. The study population in the 2 groups was comparable. Information on concomitant therapies was not reported. The publication inconsistently reported the study's observation period as 12 weeks or 3 months, i.e. the outcomes were recorded directly at the end of treatment without follow-up. Hereinafter, this survey time point is referred to as 3 months.

The Ziegelmann 2019 study [18] was conducted at a clinic in the United States from October 2017 to June 2019. A total of 110 individuals were randomized. In 97% of the randomized patients, the disease onset was more than 3 months ago (criterion for defining the stable phase in the study). The mean age was around 58 years, and the average curvature of the penis was 45 degrees, which corresponds to a moderate curvature. People with a stretched penis length of less than 7 cm or severe diabetes were excluded. There were no other exclusion criteria, e.g. with regard to the type of penile deformation, previous treatments, or erectile function. Randomization was carried out at equal rates into a control group without treatment and 3 intervention groups with different wearing frequencies (once, twice or three times per day, each with a wearing time of 30 minutes). The traction device under investigation is characterized by the fact that during traction, the penis can be stretched in a straight direction as well as bent in the opposite direction of the curvature. The 3 intervention groups were combined for the analysis of most outcomes. For the randomized controlled study phase, the duration of treatment was 3 months. The observation period of the study was 3 months, i.e. the outcomes were recorded directly at the end of treatment. This was followed by a 6-month, non-randomized study phase in which traction therapy was available to patients in both study groups [19]. The daily duration of use was at the patients' own discretion. The majority of the outcomes of this study phase were surveyed at 6 months. However, there was a significant proportion of missing data: With regard to the penile curvature outcome in the intervention group, data were available for only 57% of the originally randomized participants (47 out of 82) at 6 months. The majority of these patients continued traction therapy during the follow-up period. From the original control group, data were available for 61% of the randomized participants (17 out of 28). Because at 6 months, all participants in the original control group had also used traction therapy (treatment switching), no controlled design was in place any longer for this study phase. At 9 months, data were available from only 47 patients (57%) in the original intervention group and 16 patients (57%) in the original control group. Both the substantial proportion of missing data and the lack of a control group remaining without traction therapy rendered the data at 6 and 9 months unusable.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 2 studies. Table 2 presents an overview of the data available on patient-relevant outcomes from the included studies.

In the outcome category of **morbidity**, usable data were available for the outcomes of penile deformation, pain, sexual function, and symptom burden.

In order to depict **penile deformation** in its various dimensions, data on 2 associated outcomes were taken into account in order to characterize the higher-order outcome. The

2 outcomes were reduction in penile curvature caused by IPP and reduction in penile shortening associated with IPP.

The 2 included studies (Moncada 2019, Ziegelmann 2019) each report data on the outcome of penile curvature. The data reported in the Moncada 2019 study were usable. In the Ziegelmann 2019 study, a distinction was made between primary and combined penile curvature. In the latter case, the sum of both angular degrees was formed in the case of multiplanar, i.e. multiple, curvatures. For both operationalizations, the proportions of study participants excluded from the analysis differed by more than 20 percentage points between the groups, rendering these data unusable for the benefit assessment.

The data reported in both studies on the outcome of penile shortening, operationalized as mean change in stretched penile length, were deemed unsuitable for deriving any conclusion on benefit. (The results on this outcome are presented as supplementary information in Section A3.5 of the full report.) Data on the outcome of penile shortening would be suitable for drawing a conclusion on benefit, provided that the change in relation to the normal range (defined in the literature as 2.5 times the standard deviation [23]) can be assessed: Specifically, the data should reflect whether the change represents penile shortening within the normal range, a change from a previously abnormal penile length towards the normal range, or a change from a previously normal penile length towards an abnormal penile length. The data reported in the studies did not meet this requirement.

The outcome of **pain** was recorded in both studies using Peyronie's Disease Questionnaire (PDQ), Penile Pain domain. The data from both studies were usable.

The (superordinate) outcome of **sexual function** was also analysed in a differentiated manner (similar to the outcome of penile deformation) and characterized by the 2 subordinate outcomes of erectile function and problems during sexual intercourse.

Data on erectile function were available from both studies. The data from both studies were collected using the International Index of Erectile Function (IIEF) instrument, which consists of the following 5 domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The IIEF primarily aims to record erectile function, so that all domains of the IIEF were assigned to the outcome of erectile function. The Moncada 2019 study contained usable data on the erectile function domain but did not survey the other domains. The Ziegelmann 2019 study reported data on all 5 domains of the IIEF. Since in the Ziegelmann 2019 study, the between-group difference in the proportions of excluded study participants was more than 20 percentage points, the data were unusable for the benefit assessment. As there were no usable data on the IIEF domains of orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, the patient relevance of these domains was not examined.

Data on the second secondary outcome, problems during sexual intercourse (recorded using the PDQ, Physiological and Physical Symptoms domain), were reported in both studies. Implausible values were reported for this outcome in the Moncada 2019 study: The maximum values reported at baseline were outside the possible range of values according to the scoring instructions [24]. For example, the maximum values reported for the outcome of problems during sexual intercourse at baseline were 26 points for the intervention group and 28 points for the control group, although a maximum of 24 points is planned for this domain [24]. This also called into question the confidence in the other reported results for this outcome, e.g. the mean difference (MD). For this reason, the data on this outcome were unusable. The Ziegelmann 2019 study data on this outcome were usable.

Data were available in both studies on the outcome of **symptom burden** (assessed using the PDQ, Symptom Bother domain). In the Moncada 2019 study, the reported maximum values (as for the outcome of problems during sexual intercourse) were outside the possible value range and were therefore implausible. Due to the lack of confidence in the reported values, all results for this outcome were unusable. The data from the Ziegelmann 2019 study were usable.

No data were reported for the outcome of **mental health problems**. Conceivable would be, for example, data on depression or anxiety disorders [11].

Data on the outcome of **health-related quality of life** were likewise not reported in either of the 2 studies.

For the outcome category of **side effects**, analysable data were available in both studies for the 3 outcomes of serious adverse events (SAEs), study discontinuations due to adverse events (AEs), and non-serious AEs. The Moncada 2019 study data on side effects were collected via a diary kept by study participants during the study. In the Ziegelmann 2019 study, specific, non-serious AEs which could be expected in connection with traction therapy were actively surveyed at the 3-month time point.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes										
	Morbidity							QoL	Side effects		
	Penis deformation			Sexual function							
	Penile curvature	Penile shortening[a]	Pain[b]	Erectile function[c]	Problems during sexual intercourse[d]	Symptom burden[e]	Mental health problems	Health-related quality of life	SAEs	Study discontinuations due to AEs	Non-serious AEs
Moncada 2019	●	○	●	●	○	○	–	–	○	●	●
Ziegelmann 2019	○	○	●	○[f]	●[g]	●	–	–	●	●	●[h]

●: Data were reported and usable.

○: Data were reported but unusable for the benefit assessment.

-: No data were reported (no further information) / The outcome was not surveyed.

a. The data reported on this outcome in the publications are presented in addition below.
b. Recorded using PDQ, Penile Pain domain.
c. Recorded using IIEF; data on the erectile function domain were reported in the Moncada 2019 study. The Ziegelmann 2019 study reported data on all 5 domains of the IIEF, which were unusable for the benefit assessment; due to a lack of usable data, the domains other than the Erectile Function domain were not examined with regard to their patient relevance.
d. Recorded using PDQ, Psychological and Physical Symptoms domain.
e. Recorded using PDQ, Symptom Bother domain.
f. Further data on the outcome of erectile function (Sexual Encounter Profile, question 3 [on erection duration]) were unusable for the benefit assessment.
g. Further data on the outcome of problems during sexual intercourse (Sexual Encounter Profile, question 2 [on penetration ability], vaginal intercourse in the previous 3 months, and separately analysed questions 12 and 14 of the PDQ) were unusable for the benefit assessment.
h. The publication described these AEs as mild and transient.

AE: adverse event; IIEF: International Index of Erectile Function; PDQ: Peyronie's Disease Questionnaire; QoL: health-related quality of life; SAE: serious adverse event

4.4 Assessment of the risk of bias of the results

The risk of bias for both included studies was categorized as high across all outcomes (see Section A3.2.2 of the full report). This was because the generation of the randomization sequence and the masking of group allocation were described inadequately or not at all. Furthermore, patient blinding was not possible in either study. The Ziegelmann 2019 study did not reveal any shortcomings with regard to the criterion of reporting bias. For the Moncada 2019 study, in contrast, the presence of reporting bias was classified as unclear for several reasons: The study was not recorded in any study registries. Other than in the publication, no

information was available on analyses planned a priori, e.g. in the form of a study protocol. In addition, results were missing for a Cox proportional hazard analysis mentioned in the methods section of the publication to identify factors predictive of treatment success. With regard to the lack of other aspects which might be relevant for the risk of bias, the Moncada 2019 study suffers from several shortcomings: The publication itself contains several pieces of information which are partly implausible. (For details, see 4.3 on the sexual function outcome.) Furthermore, results were reported in an unclear and inconsistent manner, e.g. with regard to the analysis stratified by wearing time for the outcome of penile curvature: In the publication, results were reported for wearing durations of less than 4 and more than 6 hours daily – however, it remained unclear whether there was a third stratum for a wearing time of at least 4 to a maximum of 6 hours daily; furthermore, information on the number of patients included per stratum was missing. In addition, some of the results reported in the publication contain errors. For example, Figure 4 and the body of the text incorrectly report a 41.1% reduction in curvature for the intervention group. According to the mean values provided in the figure and in the text, the curvature is reduced by 31.2 angular degrees to 41.1 angular degrees, representing a reduction by 43.2%. Another point of criticism concerns the incomplete presentation of results, e.g. there was a lack of information on MD, standard deviation, or p-values, and for many outcomes (erectile function, problems with sexual intercourse, symptom burden, side effects), results were reported only for the intervention group.

The high risk of bias across outcomes directly transferred to the outcome-specific risk of bias for the results in both studies, so that no further evaluation was carried out in this regard.

4.5 Results on patient-relevant outcomes

Based on the randomized design, combined with a high risk of bias across outcomes, the results of both included studies are subject to a moderate qualitative certainty of results across all outcomes.

4.5.1 Results on the outcome of penile deformation

Usable data on the outcome of **penile curvature** were available from the Moncada 2019 study. The change in penile curvature was measured in angular degrees using a goniometer after a pharmacological erection was induced by an injection of 20 µg alprostadil. The survey was blinded. The mean value calculated from 3 consecutive measurements was used in each case. A statistically significant difference in favour of traction therapy (MWD -28.8 degrees; $p < 0.05$) was found immediately after the 3-month treatment period.

In the Ziegelmann 2019 study, the mean change in (primary) penile curvature at 3 months after an erection pharmacologically induced using alprostadil, papaverine, and phentolamine was measured in percent and angular degrees: professional medical photographers took

pictures of the penis following a standardized protocol. The curvature was then assessed in a blinded manner using the images. The data were unusable due to the between-group difference in the proportion of excluded study participants (> 20 percentage points). The publication reveals the number of patients in the intervention group who exhibited an improvement in primary penile curvature by at least 20 degrees (17 out of 62). The same information is not available for the control group. Even in a scenario where none of the patients in the intervention group with a missing follow-up measurement and 0 or 1 patient (out of 28) in the control group achieved a corresponding improvement, the analysis would result in a statistically significant effect in favour of traction therapy.

In both studies, the effect of traction therapy regarding a reduction in penile curvature is based on a study phase of only 3 months without follow-up. No usable data are available on the presence and nature of any changes in penile curvature after the 3-month treatment period. Ultimately, the available data fail to clarify whether and to what extent the achieved reduction in penile curvature will be maintained in the long term. Overall, no hint of benefit of traction therapy was derived due in particular to the lack of usable data on longer-term effects for the outcome of penile deformation.

4.5.2 Results on the outcome of pain

Usable data on the outcome of **pain** were available from both included studies (Moncada 2019, Ziegelmann 2019). The extent of penile pain in the flaccid and erect state and during vaginal intercourse was assessed in both studies using a questionnaire (PDQ, Penile Pain Domain), analysed as the mean change in score values compared to baseline values. Neither study reported a statistically significant between-group difference.

Overall, this results in no hint of benefit or harm of traction therapy for the outcome of pain.

4.5.3 Results for the sexual function outcome

The higher-order outcome of sexual function includes both the outcome of erectile function and the outcome of problems during sexual intercourse.

For the outcome of **erectile function** – surveyed via the IIEF questionnaire – the Moncada 2019 study provided usable data in the Erectile Function domain, analysed as the mean score change compared to baseline. There was no statistically significant between-group difference.

The Ziegelmann 2019 study provided usable data on the outcome of **problems with sexual intercourse** – measured using the PDQ, Psychological and Physical Symptoms domain – analysed as the mean score change compared to baseline. There was no statistically significant between-group difference.

Overall, this results in no hint of benefit or harm of traction therapy for the higher-order outcome of sexual functioning.

4.5.4 Results for the symptom burden outcome

The Ziegelmann 2019 study provided usable data on the outcome of **symptom burden** – measured using the PDQ, Symptom Bother domain – analysed as the mean score change compared to baseline. There was no statistically significant between-group difference.

Overall, this results in no hint of benefit or harm of traction therapy for the outcome of symptom burden.

4.5.5 Results for the mental impairment outcome

No results on this outcome were reported in the included studies.

4.5.6 Results for the outcome of health-related quality of life

No results on this outcome were reported in the included studies.

4.5.7 Results on the outcome of side effects

Side effects data were available from both studies. These were differentiated into AEs, study discontinuations due to AEs, and non-serious AEs.

For the outcome of **SAEs**, results from both studies, in each case for the intervention group, were usable. Although AEs were not explicitly reported in the Moncada 2019 study, the publication states that no SAEs occurred (in the intervention group), as all AEs which occurred were mild and short-term events. For the intervention group, Ziegelmann 2019 explicitly reports that no SAEs, including no deaths, occurred. No data were reported for the comparator group. In either study, it is unlikely for any SAEs or deaths to have occurred in the comparator group without treatment or for any SAEs to have occurred but not have been reported. Therefore, no hint of harm was derived for the outcome of SAEs.

Results on the outcome of **study discontinuation due to AEs** are available for both studies' intervention groups. In Moncada 2019, 3 out of 46 participants discontinued the study due to AEs (6.5%), while in Ziegelmann 2019, there were no study discontinuations due to AEs. The cases of study discontinuation described in Moncada 2019 were 2 patients with oedema of the glans and 1 patient with pain on the penile shaft as a result of excessive use of traction therapy. In all 3 patients, the AEs were successfully conservatively treated within 2 days of interrupting the traction therapy. Based on these results, no hint of harm was therefore derived for the outcome of study discontinuations due to AEs.

For the outcome of **non-severe AEs**, data were available from both studies, but only from their intervention groups. Moncada 2019 reported the overall rate of AEs for the intervention group, summarizing them as mild, transient, and tolerable (43%). According to the publication, the events mainly involved localized pain and numbness of the glans. In addition to reporting the overall rate of non-serious AEs (53.7%), the Ziegelmann 2019 study provides results on individual AEs, describing them as mild and transient. Some of these were events of unclear origin, which could be linked to either the disease process or to traction therapy (e.g. redness or loss of sensation of the penis). Other events are more likely to be attributable to traction therapy (e.g. skin rash caused by tape). Due to the unsystematic recording, combined with a lack of data on the comparison group, it was not possible to draw any conclusions on an effect for the outcome of non-serious AEs.

In summary, there was no hint of harm from traction therapy compared to no treatment for the individual side effects outcomes.

4.6 Overall evaluation of the results

Evidence map

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

Table 3: Evidence map regarding patient-relevant outcomes

Morbidity					QoL	Side effects		
Penile deformation	Pain	Sexual function	Symptom burden	Mental health problems	Health-related quality of life	SAEs	Study discontinuations due to AEs	Non-serious AEs
⇔	⇔	⇔	⇔	–	–	⇔	⇔	(⇔)

⇔: no hint, indication, or proof
(⇔): no hint due to insufficient data
-: no data reported

AE: adverse event; QoL: health-related quality of life; SAE: serious adverse event

Assessment of the volume of unpublished data

No relevant study without reported results was found (see Section A3.1.4 of the full report). Therefore, the certainty of results was not reduced in the present benefit assessment.

Weighing of benefits versus harm

For the outcomes of penile deformation, pain, sexual function, and symptom burden, there is no hint of benefit from traction therapy compared to no treatment. No data are available for the outcomes of mental health problems or health-related quality of life. The available side effects data result in no hint of harm from traction therapy compared to no treatment.

In the overall assessment across all outcomes, no hint of benefit or harm from traction therapy compared to no treatment was derived. The main reasons for not deriving any benefit are (a) the in part very poor methodological quality of the 2 primary studies (for details see Section 4.4) and (b) the inadequate patient follow-up observation after the end of the 3-month treatment.

Rating of the potential for a necessary treatment alternative

Given the available results on the reduction of penile curvature by the end of the 3-month treatment phase, it can be concluded that traction therapy represents a necessary alternative treatment for IPP compared to no treatment. This conclusion rests on the fact that no conservative therapies which have been proven effective are currently available for the treatment of IPP in Germany. Traction therapy might therefore represent an alternative to no treatment for those patients who are not (yet) eligible for surgical treatment due to the stage of their disease, or for patients who refuse invasive surgery due to the associated risks and for whom therefore, no effective treatment options are currently available in Germany.

4.7 Key characteristics of a testing study

In the comparison of traction therapy versus no treatment, the potential of the former representing a necessary treatment alternative was derived. No ongoing studies were identified which would be generally suitable for proving a benefit of the method. The key characteristics of a testing study are therefore outlined below.

Study type

A 2-arm, multicentre RCT with blinded outcome recording should be conducted. The study should test the superiority of traction therapy over no treatment with regard to patient-relevant outcomes.

Target population

The study should enrol adults aged 18 years and older with IPP requiring treatment in an acute or stable phase of the disease. A particularly suitable population would be people who are not (yet) eligible for surgical treatment due to their stage of disease or people who refuse invasive surgery due to the associated risks. Participants should exhibit at least moderate penile curvature, i.e. a curvature of over 30 degrees [21,22]. Implementing special restrictions regarding the type of curvature (e.g. uniplanar versus multiplanar) does not appear to be

meaningful. Persons whose penile curvature is associated with penile deformities, such as an hourglass phenomenon or retraction of the tunica albuginea, may also be included. ED should not be a general reason for exclusion.

Details of the inclusion and exclusion criteria as well as of the diagnostics are to be determined as part of the specific study design.

Experimental intervention and comparator intervention

The experimental intervention comprises traction therapy with a bar expander system. Currently available traction devices offering straight extension are suitable for this purpose. A treatment period of at least 3 months is suggested. Three months is the treatment period of the studies from which the potential of the method was derived. Following the treatment phase, intervention-group participants should be free to decide whether or not to continue traction therapy in order to reflect the expected application in routine care. The instructions for use of the device which was used in an included study and is available in Germany do not explicitly detail the design of a long-term treatment regimen [25]. The duration and intensity of use should be surveyed for the entire duration of the study. Qualified professionals should instruct study participants regarding the use of the employed device.

The comparator intervention is a waiting list because there are currently no conservative therapies which have been proven effective and are available in Germany for the treatment of IPP. Alternatively, consideration can be given to providing the comparator group with instructions for manual therapy, which is also used to accompany CCH injections [26]. Manual therapy would not be expected to have any relevant effects, but such minimal therapy could increase the motivation to participate.

Concomitant therapies for the treatment of IPP or ED can be carried out in both arms but should be documented.

Outcomes

One of the 2 co-primary outcomes is to be the proportion of people exhibiting a relevant change in penile curvature at 12 months after randomization. (In the case of multiple curvatures, the sum of the curvatures can also be recorded.) The specific definition of the response criterion is to be determined by the independent scientific institution. Penile curvature is suitable as a co-primary outcome because it is the leading symptom of the disease and traction therapy is aimed directly at reducing it. However, the ultimate goal of IPP treatment is to bring about a noticeable change in the symptoms associated with penile curvature for those affected. Therefore, an improvement in symptoms associated with penile curvature should be assessed as the other co-primary outcome, also at 12 months after randomization. In principle, this may involve the outcomes of sexual function and general

symptoms, for example. (In CCH studies, the Global Assessment of Peyronie's Disease [GAPD] instrument was used for this purpose [26,27])

Potential secondary outcomes include mental health problems, symptom burden, health-related quality of life, and pain. In addition, (serious) AEs should be systematically recorded. The change in penile curvature should also be recorded as a continuous target variable. In addition, it is common practice in studies on the treatment of IPP to record the change in penile shortening (for an assessment of the patient relevance of this outcome, see Section 5.4). It would also be desirable to record how many people drop out of the study in order to undergo surgery, as avoiding surgery represents a relevant therapeutic goal of conservative treatment.

Study design

The aim of the study is to prove that (1) penile curvature is reduced to a relevant extent and that (2) this is accompanied by a noticeable improvement in the symptoms associated with penile curvature. It is therefore proposed to define 2 (co-)primary outcomes and to test these as part of a hierarchical hypothesis test. In case of an organized hypothesis test, an adjustment of the usual error level is not necessary.

The following comments on case number estimates are not to be understood as binding information, but rather as approximate estimates of the required number of cases. Binding case number planning must be carried out as part of the specific study planning.

With a study of 100 to 200 people, it would be possible (assuming a significance level of 5% for 2-sided testing and a power of 90% as well as a probability of 10% for a relevant improvement in penile curvature or a relevant improvement in symptoms in the control group) to show a statistically significant advantage with regard to a relevant improvement in penile curvature or a relevant improvement in symptoms if the true effect had a size of OR = 5.3 (100 people) or OR = 3.5 (200people). In case of 100 participants, this would correspond to responder rates of 10% in the control group and 37% in the intervention group, or, in case of 200 participants, 10% in the control group and 28% in the intervention group.

In order to increase motivation to participate, a 2:1 randomization ratio would be conceivable. This would require a moderate increase in the number of cases.

An observation period of at least 12 months is proposed from study inclusion in order to check whether traction therapy leads to lasting improvements. This is in line with expert recommendations for conducting clinical trials on IPP, which suggest an observation period of at least 12 months, preferably 18 months [28].

Stratified randomization (especially according to disease phase, curvature severity, and study centre) should be considered when planning the study. When collecting data, implementing repeated measurements appears sensible (e.g. measurements at 3-month intervals), particularly in view of potential missing values at later points in time. In addition, an analysis should take into account stratification factors as well as any other prespecified potential effect modifiers.

The study must be conducted in compliance with the rules of Good Clinical Practice (GCP).

Study costs

For studies with moderate case numbers and expenditures, study-specific costs of around € 5500 per person can be estimated. Based on these assumptions, study costs of between € 550,000 and€ 1.1 million are to be expected.

The cost estimates are for guidance only and are not suitable as a basis for contractual cost agreements. The estimates of study costs used here generally apply to studies for which the necessary infrastructure must be completely established anew. The utilization of an existing data structure as implemented in a register-based RCT could reduce costs.

Prospects of success for testing

Based on the epidemiology of the disease, it seems feasible to recruit 100 to 200 people to participate in a study: IPP has a comparatively high prevalence, so enough people should be available to take part in a study. (Most prevalence estimates are in the single-digit percentage range.) Several locations in Germany which offer andrological consultations with counselling on and treatment of IPP are eligible as study centres. It is difficult to estimate the proportion of people who would agree to participate in such a study. On the one hand, study participation involves potential access to a treatment which is currently not available within the framework of SHI care. On the other hand, IPP sufferers can also decide to purchase a traction device at their own expense outside of study participation (the costs of bar expander systems for the treatment of IPP ranges around € 160 to € 350, depending on the device).

Assuming, for example, 4 study centres with an average of around 100 new patients per year and centre who would be eligible for the study, it seems realistic to recruit 100 to 200 people within a year – assuming that existing patients are included in the study alongside new patients. When including preparation, follow-up, and analysis, a study duration of around 3 years should be aimed for.

When planning the study, it should also be borne in mind that, due to the complexity of the treatment, there is an increased probability of intervention group participants discontinuing the study intervention. It should be examined how people in these cases can be motivated to participate at least in outcome surveys (e.g. regular contacts), even if they discontinue

treatment. Control-group participants might be motivated to continue the study by instructing and motivating them to use manual therapy.

5 Classification of the assessment result

5.1 Shortcomings of the Moncada 2019 study

The Moncada 2019 study suffers from substantial shortcomings in several respects: Due to the fact that no registry entry and no study protocol were available, there was also no information on analyses planned a priori. Furthermore, the publication is of poor quality: Results were not fully reported. In addition, it contains implausible values and incorrect and unclear information on study results. Authors' requests for clarification of the available data were not answered.

5.2 Long-term effects of traction therapy

The 2 included studies investigated the effects of traction therapy immediately following the 3-month treatment in each case. In view of the efforts associated with treatment, patients cannot be expected to continue therapy in the long term at the same intensity as during the studies' treatment phase. A relevant question is therefore what happens if the therapy is discontinued or continued at much lower intensity: There was no follow-up for Moncada 2019. The study authors themselves concede that they did not investigate the sustainability of the achieved improvement or a possible return of the curvature after the end of treatment. Due to the elastic nature of penile tissue, they deem it reasonable to expect that the curvature could reappear to a certain extent. Although Ziegelmann 2019 conducted a follow-up at 6 and 9 months after randomization [19], a substantial proportion of the data were missing at these points in time, and almost complete treatment switching was implemented. The 2 studies therefore do not allow any conclusions to be drawn about the sustainability of the observed effect of traction therapy on the reduction of penile curvature. Against this background, this report did not derive any hint of benefit with regard to the outcome of penile curvature despite the statistically significant effect immediately after the end of treatment.

5.3 Patient relevance of the penile curvature outcome

The main characteristic of IPP is deformation of the penis, with penile curvature representing the main symptom [6,29]. Penile curvature, particularly when erect, is a symptom of IPP which is directly perceptible for those affected and is often associated with other symptoms: It is plausible that a significant curvature in the context of IPP has an effect on sexual function [22], and this was also discussed in the interview with those affected. Several studies have described this curvature as also being associated with mental health problems, e.g. anxiety disorders, a disturbed self-image, or depression [11,30,31]. In this report, the outcome of penile curvature – defined as a change (reduction or increase) in curvature which previously developed due to IPP – is deemed a patient-relevant outcome.

It would be problematic for the assessment to disregard the data on the outcome of penile curvature, in part due to the fact that changes in sexual function can be recorded only by some

of the patients, namely the sexually active ones. (This applies in particular to PDQ, see Section A4.3.1. of the full report) The penile curvature outcome, in contrast, was generally suitable to be surveyed in all patients.

Certainly, a change in curvature is patient relevant only if the curvature changes to a relevant extent – i.e. to an extent which is sufficiently certain to be accompanied by a noticeable change in symptoms. According to Ziegelmann et al. [29], a fundamental difficulty in defining a clinical relevance threshold is that the degree of curvature which leads to functional limitations, i.e. prevents satisfactory sexual intercourse, varies greatly from person to person and depends on subjective perception. In a validation study on the PDQ, an improvement in curvature by at least 20% to less than 50% at the individual level was described as a minor to moderate improvement [32]. Some studies on traction therapy, e.g. Ziegelmann 2019, report results on individual curvature reduction, operationalized as a reduction by at least 20 degrees. In the approval studies comparing CCH injections versus placebo, a statistically significant between-group difference in curvature improvement by 7.7 degrees (equivalent to 15.8 percentage points) was associated with, among other things, a statistically significantly higher proportion of people receiving CCH treatment who reported "minor but important improvements" in their disease (equivalent to ≥ 1 point on the GAPD instrument) [26].

The Moncada 2019 study reported a mean penile curvature around 70 degrees at baseline, which corresponds to a severe curvature [21,22], and around 40 degrees at the end of the study in the patients with traction therapy, which corresponds to moderate curvature (and a reduction in curvature by around 43%). In the control group, the penile curvature at the end of the study was around 66 degrees (corresponding to a reduction in curvature by around 4%). In the between-group comparison, the reduction in curvature was -28.8 degrees. No responder analyses are available for the study. The improvement in penile curvature under traction therapy in the Moncada 2019 study is presumably a clinically relevant change, although it is currently unclear at what level of change (both at the individual level and in the between-group comparison) a reduced curvature is sufficiently large to be deemed clinically relevant.

5.4 Patient relevance of the outcome of penile shortening, operationalized as stretched penis length

For the higher-order outcome of penile deformation, data were presented on the outcome of penile shortening, operationalized as stretched penis length. Stretched penis length is subject to a large natural variance (5th and 95th percentile: approx. 10 to 16.5 cm [23]). In order to ensure the relevance of an observed change, standard values were used as a guide. However, the available data did not allow any conclusions to be drawn as to the proportion of patients for whom the values for stretched penis length changed from outside the normal range (deviation of the mean stretched penis length by more than 2.5 standard deviations) to within

the normal range or vice versa. In both studies, the data on penis shortening were reported only as mean stretched penis length and were therefore not deemed suitable for deriving a benefit.

From the patient's perspective, IPP-related shortening of the penis per se – i.e., irrespective of the normal range – may play a relevant role. A qualitative study [31] shows that penis length can be closely linked to self-esteem and sexual function in patients with IPP. In addition, penis length is a clinically relevant factor in the selection of a suitable surgical procedure: If penis length is no longer sufficient for performing a tunica-shortening surgical procedure, more invasive and riskier surgical procedures are recommended. Against this background, results on penis shortening, operationalized as mean stretched penis length, were also presented. If improvements in penis shortening lead to a relevant improvement in functional impairment or individual distress during the course of treatment, this should be reflected in the corresponding patient-relevant outcomes (e.g. problems during sexual intercourse or symptom burden).

5.5 Limited sensitivity to change with regard to the pain outcome

For the Penile Pain domain, validation studies [24,32] for the PDQ show that the mean values in patients with IPP in the stable phase are in the lower range of the theoretically achievable value range and thus exhibit limited sensitivity to change. This is due to the fact that only a small proportion of people with IPP suffer from pain in the stable phase of the disease [33]. In both included studies with data on the outcome of pain, either the majority (Ziegelmann 2019) or all patients (Moncada 2019) were recruited in the stable phase, which is reflected by the low mean scores at baseline. The Moncada 2019 study explicitly excluded patients with severe pain. It was therefore to be expected that no statistically significant effects in favour of traction therapy could be achieved with regard to the pain outcome. A patient population with a greater percentage of people suffering from pain, i.e. primarily people in the acute phase, would therefore be more suitable for demonstrating potential favourable effects of traction therapy on penile pain.

5.6 Limited sensitivity to change with regard to the outcome of erectile function

Data on the outcome of erectile function were available from the Moncada 2019 study. An exclusion criterion in this study was existing ED at baseline (threshold value: < 21 points in the erectile function domain of the IIEF, value range 0-30). The data on mean scores and ranges at baseline confirmed that the patients had, at most, mild forms of ED: the mean value in the group with traction therapy was 23.6 points (min; max: 22; 27) and in the group without treatment, 22.9 points (min; max: 21; 28). A low sensitivity to change was therefore also to be assumed for the outcome of erectile function, which is accompanied by a low probability of statistically significant effects in favour of traction therapy. In order to be able to demonstrate

potential favourable as well as potential unfavourable effects of traction therapy, it would be more prudent to include patients in a study regardless of their erectile function.

5.7 Comparability of the traction devices included in the studies

Both devices used for traction therapy in the included studies are bar expander systems. The devices differ in particular with regard to the type of stretching and the intended daily duration of use:

While the device used in the Moncada 2019 study (PeniMaster Pro) provides for straight expansion, the device used in the Ziegelmann 2019 study (RestoreX) combines straight expansion with counter-bending at the site of the plaque.

In the Moncada 2019 study, the target daily duration of use after an adaptation phase was 6 to 8 hours/day with regular breaks. The instructions for use specify a target wearing time for the PeniMaster Pro device of at least 3 hours, ideally 8 hours a day (with a regeneration break of half an hour after 3 hours at the latest) [25]. The target wearing time in the Ziegelmann 2019 study was 30 minutes once to three times a day, depending on the study arm. For the RestoreX device, the instructions for use recommend 2 daily treatment sessions of 30 minutes each (15 minutes each of straight extension and counter-bending); following a 3-month treatment phase, 1 treatment session of 30 minutes per week is then recommended as maintenance therapy [34]. The recommended daily wearing time therefore differs by a factor of about 6 (1 h or 6 h). It is to be expected that the different treatment requirements of the devices will affect treatment compliance.

Furthermore, the devices differ in terms of their availability on the German or European market: The majority of the available traction devices, including the PeniMaster Pro device used in the Moncada 2019 study, have a CE certificate and are therefore available on the German market. However, the RestoreX device developed in the United States is unavailable on the European market due to a lack of CE certification. The manufacturer states on its website that CE certification is being sought [35].

Based on the available data from both studies, it was impossible to test a possible effect modification due to the device type. However, the results of both studies point in the same direction with regard to a potential benefit, namely in favour of traction therapy administered with the respective device. The studies observed similar results on side effects: Mild, transient AEs occurred in around 43% of patients in Moncada 2019 and around 54% of patients in the intervention group in Ziegelmann 2019. The rate of discontinuation due to AEs tended to be higher in the Moncada 2019 study (3 out of 46) than in the Ziegelmann 2019 study (0 out of 82); overall, AEs caused only a few study participants to discontinue the study.

The literature categorizes both traction devices with straight extension alone and the traction device with counter-flexion (RestoreX) as traction therapy. This further supports the idea that the same mechanism of action is used by both types of devices and that the different products for implementing the method are fundamentally comparable in terms of their potential benefits and harms. A potential marketing authorization of RestoreX for the European market should be taken into account when planning a possible testing study.

5.8 Duration of illness of the patients included in the studies

In principle, traction therapy can be used in both the stable and acute phases of the disease [7,18,25,36].

Only patients in the stable phase were included in the Moncada 2019 study. The median duration of illness in the intervention and control groups was 19 and 20 months, respectively, with a standard deviation of 6 and 5 months. Both acute-phase and stable-phase patients were included in the Ziegelmann 2019 study. The majority of the patients were in the stable phase of disease. The mean duration of illness in the intervention and control groups was 46 and 52 months, respectively, with a standard deviation of 45 and 33 months. The fact that fewer acute-phase patients were included may be due to various reasons, e.g. the time window being shorter for the acute phase than for the stable phase and thus the prevalence of IPP patients in the stable phase being higher of those than in the acute phase. The available studies do not provide any data on a possible effect modification which would suggest qualitatively different effects with regard to the disease phase. The influence of the disease phase on the effect of traction therapy should be investigated as part of a potential testing study.

5.9 Appropriateness of the comparator intervention

The 2 included studies compared traction therapy versus no treatment. No suitable studies were conducted on other potential research questions (e.g. traction therapy versus surgery).

In principle, alternative comparator interventions would be conceivable. However, there is currently no recommended standard therapy across all phases of the disease. The therapies currently used are particularly based on phase of disease. With regard to the *acute* phase, there is currently no evidence for an effective therapy aimed at halting the progression of the disease. Surgical procedures are primarily recommended for the *stable* phase, as the intralesional injections mentioned in the guidelines as possible conservative therapies are rarely used in Germany, either due to a lack of authorization for the therapeutic indication [3] or due to the authorization having been withdrawn [14]. The choice of surgical technique depends on penis length, degree of curvature, erectile function, and patient preference [7].

The EAU guideline [7] and a publication on the clinical treatment pathway for IPP based on 3 guidelines [36] recommend traction therapy in particular for people in the acute phase, to be implemented in the treatment cascade prior to surgery. Contrary to this recommendation, the majority of the included studies recruited men in the stable phase, although at least the Ziegelmann 2019 study made no restriction with regard to the disease phase. This contradiction might be due to the fact that even in the stable phase, patients tend to prefer conservative therapies such as traction therapy due to the potential complications associated with surgical interventions and ideally wish to avoid surgery. Against this background, the comparison of traction therapy versus no treatment is deemed appropriate.

6 Conclusion

Two RCTs were included to answer the research question. Both studies compared penile traction therapy versus no treatment.

With regard to the outcome of penile deformation, the data showed that. in the short term, i.e. immediately after the 3-month treatment, traction therapy reduced the curvature of the penis caused by the disease more than no treatment. However, no usable data were available on whether this effect persists in the longer term, and no hint of benefit was derived.

No advantages were found for the outcomes of pain, sexual function, and symptom burden; this resulted in no hint of benefit of traction therapy compared to no treatment.

No data are available for the outcomes of mental health problems or health-related quality of life.

With regard to the outcome of side effects, no hint of harm from traction therapy compared to no treatment was derived on the basis of the available data.

In summary, no hint was derived for a benefit or harm from traction therapy compared to no treatment.

Based on the available results on the reduction of penile curvature at the end of the 3-month treatment phase, it can be concluded that traction therapy is a necessary alternative treatment for IPP compared to no treatment. As no ongoing studies were identified which would be fundamentally suitable for demonstrating a benefit, key characteristics for a possible testing study were outlined.

References for English extract

Please see full final report for full reference list.

1. Bilgutay AN, Pastuszak AW. Peyronie's Disease: A Review of Etiology, Diagnosis, and Management. Curr Sex Health Rep 2015; 7(2): 117-131. https://doi.org/10.1007/s11930-015-0045-y.

2. Herati AS, Pastuszak AW. The Genetic Basis of Peyronie Disease: A Review. Sex Med Rev 2016; 4(1): 85-94. https://doi.org/10.1016/j.sxmr.2015.10.002.

3. Hauptmann A, Wagenlehner FME, Diemer T. Aktuelle Therapie der Induratio penis plastica (IPP). Der Urologe 2018; 57(9): 1139-1152. https://doi.org/10.1007/s00120-018-0752-x.

4. Nehra A, Alterowitz R, Culkin DJ et al. Peyronie's Disease: AUA Guideline. J Urol 2015; 194(3): 745-753. https://doi.org/10.1016/j.juro.2015.05.098.

5. Piraino J, Chaudhary H, Ames K et al. A Consistent Lack of Consistency in Defining the Acute and Chronic Phases of Peyronie's Disease: A Review of the Contemporary Literature. Sex Med Rev 2022; 10(4): 698-713. https://doi.org/10.1016/j.sxmr.2022.08.001.

6. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. J Urol 2006; 175(6): 2115-2118; discussion 2118. https://doi.org/10.1016/s0022-5347(06)00270-9.

7. European Association of Urology. EAU Guidelines on Sexual and Reproductive Health [online]. 2022 [Accessed: 23.08.2023]. URL: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Sexual-and-Reproductive-Health-2023.pdf.

8. Schwarzer U, Sommer F, Klotz T et al. The prevalence of Peyronie's disease: results of a large survey. BJU Int 2001; 88(7): 727-730. https://doi.org/10.1046/j.1464-4096.2001.02436.x.

9. Stuntz M, Perlaky A, des Vignes F et al. The Prevalence of Peyronie's Disease in the United States: A Population-Based Study. PLoS One 2016; 11(2): e0150157. https://doi.org/10.1371/journal.pone.0150157.

10. Bella AJ, Lee JC, Grober ED et al. 2018 Canadian Urological Association guideline for Peyronie's disease and congenital penile curvature. Can Urol Assoc J 2018; 12(5): E197-209. https://doi.org/10.5489/cuaj.5255.

11. Kuja-Halkola R, Henningsohn L, D'Onofrio BM et al. Mental Disorders in Peyronie's Disease: A Swedish Cohort Study of 3.5 Million Men. J Urol 2021; 205(3): 864-870. https://doi.org/10.1097/ju.0000000000001426.

12. Terrier JE, Nelson CJ. Psychological aspects of Peyronie's disease. Transl Androl Urol 2016; 5(3): 290-295. https://doi.org/10.21037/tau.2016.05.14.

13. Farrell MR, Ziegelmann MJ, Bajic P, Levine LA. Peyronie's Disease and the Female Sexual Partner: A Comparison of the Male and Female Experience. J Sex Med 2020; 17(12): 2456-2461. https://doi.org/10.1016/j.jsxm.2020.08.010.

14. European Medicines Agency. Xiapex: Withdrawal of the marketing authorisation in the European Union [online]. 2020 [Accessed: 17.08.2023]. URL: https://www.ema.europa.eu/documents/public-statement/public-statement-xiapex-withdrawal-marketing-authorisation-european-union_en.pdf.

15. Sultana A, Grice P, Vukina J et al. Indications and characteristics of penile traction and vacuum erection devices. Nat Rev Urol 2022; 19(2): 84-100. https://doi.org/10.1038/s41585-021-00532-7.

16. García-Gómez B, Aversa A, Alonso-Isa M et al. The Use of Penile Traction Devices for Peyronie's Disease: Position Statements from the European Society for Sexual Medicine. Sex Med 2021; 9(4): 100387. https://doi.org/10.1016/j.esxm.2021.100387.

17. Moncada I, Krishnappa P, Romero J et al. Penile traction therapy with the new device 'Penimaster PRO' is effective and safe in the stable phase of Peyronie's disease: a controlled multicentre study. BJU Int 2019; 123(4): 694-702. https://doi.org/10.1111/bju.14602.

18. Ziegelmann M, Savage J, Toussi A et al. Outcomes of a Novel Penile Traction Device in Men with Peyronie's Disease: A Randomized, Single-Blind, Controlled Trial. J Urol 2019; 202(3): 599-610. https://doi.org/10.1097/ju.0000000000000245.

19. Joseph J, Ziegelmann MJ, Alom M et al. Outcomes of RestoreX Penile Traction Therapy in Men With Peyronie's Disease: Results From Open Label and Follow-up Phases. J Sex Med 2020; 17(12): 2462-2471. https://doi.org/10.1016/j.jsxm.2020.10.003.

20. Mayo Clinic. Efficacy of Penile Traction Therapy Using a Novel Device [online]. 2020 [Accessed: 17.08.2023]. URL: https://ClinicalTrials.gov/show/NCT03389854.

21. Kelami A. Classification of congenital and acquired penile deviation. Urol Int 1983; 38(4): 229-233. https://doi.org/10.1159/000280897.

22. Walsh TJ, Hotaling JM, Lue TF, Smith JF. How curved is too curved? The severity of penile deformity may predict sexual disability among men with Peyronie's disease. Int J Impot Res 2013; 25(3): 109-112. https://doi.org/10.1038/ijir.2012.48.

23. Veale D, Miles S, Bramley S et al. Am I normal? A systematic review and construction of nomograms for flaccid and erect penis length and circumference in up to 15,521 men. BJU Int 2015; 115(6): 978-986. https://doi.org/10.1111/bju.13010.

24. Hellstrom WJ, Feldman R, Rosen RC et al. Bother and distress associated with Peyronie's disease: validation of the Peyronie's disease questionnaire. J Urol 2013; 190(2): 627-634. https://doi.org/10.1016/j.juro.2013.01.090.

25. MSP Concept. PeniMaster Pro Stangen-Expandersystem; Gebrauchsanleitung [online]. 2021 [Accessed: 17.08.2023]. URL: https://media.penimaster.com/Anleitung/Anleitung-DE-PeniMasterPRO.pdf#miniweb.

26. Gelbard M, Goldstein I, Hellstrom WJ et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. J Urol 2013; 190(1): 199-207. https://doi.org/10.1016/j.juro.2013.01.087.

27. Hellstrom W, Gittleman M, Tan R et al. Meaninful change in Peyronie's Disease following treatment with Collagenase Clostridium Histolyticum: Results from zwo large double blind, randomized, placebo-controlled phase 3 studies; PD22-02. J Urol 2014; 191(4S): e672. https://doi.org/10.1016/j.juro.2014.02.1854.

28. Porst H, Vardi Y, Akkus E et al. Standards for clinical trials in male sexual dysfunctions. J Sex Med 2010; 7(1 Pt 2): 414-444. https://doi.org/10.1111/j.1743-6109.2009.01623.x.

29. Ziegelmann MJ, Trost LW, Russo GI, Levine LA. Peyronie's Disease Intervention Studies: An Exploration of Modern-Era Challenges in Study Design and Evaluating Treatment Outcomes. J Sex Med 2020; 17(3): 364-377. https://doi.org/10.1016/j.jsxm.2019.11.271.

30. Nelson CJ, Mulhall JP. Psychological impact of Peyronie's disease: a review. J Sex Med 2013; 10(3): 653-660. https://doi.org/10.1111/j.1743-6109.2012.02999.x.

31. Rosen R, Catania J, Lue T et al. Impact of Peyronie's disease on sexual and psychosocial functioning: qualitative findings in patients and controls. J Sex Med 2008; 5(8): 1977-1984. https://doi.org/10.1111/j.1743-6109.2008.00883.x.

32. Coyne KS, Currie BM, Thompson CL, Smith TM. Responsiveness of the Peyronie's Disease Questionnaire (PDQ). J Sex Med 2015; 12(4): 1072-1079. https://doi.org/10.1111/jsm.12838.

33. Hellstrom WJ, Feldman RA, Coyne KS et al. Self-report and Clinical Response to Peyronie's Disease Treatment: Peyronie's Disease Questionnaire Results From 2 Large Double-Blind, Randomized, Placebo-Controlled Phase 3 Studies. Urology 2015; 86(2): 291-298. https://doi.org/10.1016/j.urology.2015.04.047.

34. PathRight Medical. RestoreX; Next Generation Penile Traction Therapy Defice; Instructions for use [online]. [Accessed: 17.08.2023]. URL: https://www.restorex.com/?s=Instructions+for+use.

35. Pathright Medical. RestoreX; Frequently Asked Questions [online]. [Accessed: 17.08.2023]. URL: https://www.restorex.com/restorex/faqs/.

36. Chung E, Gillman M, Tuckey J et al. A clinical pathway for the management of Peyronie's disease: integrating clinical guidelines from the International Society of Sexual Medicine, American Urological Association and European Urological Association. BJU Int 2020; 126 Suppl 1: 12-17. https://doi.org/10.1111/bju.15057.

37. Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

The full report (German version) is published under

https://www.iqwig.de/en/projects/n22-01.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 August 23, 2022

The following filter was adopted:

- Systematic review: Wong [37] – High specificity strategy

#	Searches
1	exp Penile Induration/
2	(peyronie* adj1 disease*).ti,ab.
3	(induratio adj1 penis adj1 plastica).ti,ab.
4	(peni* adj1 (induration* or curvature*)).ti,ab.
5	or/1-4
6	cochrane database of systematic reviews.jn.
7	(search or MEDLINE or systematic review).tw.
8	meta analysis.pt.
9	or/6-8
10	9 not (exp animals/ not humans.sh.)
11	and/5,10
12	11 and (english or german or multilingual or undetermined).lg.
13	..l/ 12 yr=2018-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Penile Induration"[mhe]
2	(peyronie* AND disease*)[Title] OR (peyronie* AND disease*)[abs]
3	(induratio AND penis AND plastica)[Title] OR (induratio AND penis AND plastica)[abs]
4	(peni* AND induration*)[Title] OR (peni* AND induration*)[abs]
5	(peni* AND curvature*)[Title] OR (peni* AND curvature*)[abs]
6	#1 OR #2 OR #3 OR #4 OR #5

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to June 28, 2023

#	Searches
1	Penile Induration/
2	peyronie*.ti,ab.
3	(peni* and curvature*).ti,ab.
4	or/1-3
5	Traction/
6	(traction* or extender*).ti,ab.
7	(restorex or penimaster or andropeyronie or phallosan).ti,ab.
8	or/5-7
9	and/4,8
10	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
11	hi.fs. or case report.mp.
12	or/10-11
12	9 not 12

2. Embase

Search interface: Ovid

- Embase <1974 to 2023 June 28>

#	Searches
1	Peyronie disease/
2	peyronie*.ti,ab.
3	(peni* and curvature*).ti,ab.
4	or/1-3
5	exp traction therapy/
6	(traction* or extender*).ti,ab.
7	(restorex or penimaster or andropeyronie or phallosan).ti,ab.
8	or/5-7
9	and/4,8
10	9 not medline.cr.
11	10 not (exp animal/ not exp human/)
12	11 not (Conference Abstract or Conference Review or Editorial).pt.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2023

#	Searches
1	[mh ^"Penile Induration"]
2	peyronie*:ti,ab
3	(peni* and curvature*):ti,ab
4	#1 or #2 or #3
5	[mh ^"Traction"]
6	(traction* or extender*):ti,ab
7	(restorex or penimaster or phallosan or andropeyronie):ti,ab
8	#5 or #6 or #7
9	#4 AND #8
10	#9 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

A.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
(Peyronie Disease OR Penile Diseases) AND (Traction OR Extender OR Restorex OR Penimaster OR Andropeyronie OR Phallosan)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

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

Search strategy
(Peyronie OR Penile) AND (Traction OR Extender OR Restorex OR Penimaster OR Andropeyronie OR Phallosan)