Study protocol of a multicentre double-blind RCT, comparing a traditional RCT with an aggregated N-of-1 trial: GAG therapy Efficacy Trial Solution for Bladder pain syndrome/Interstitial cystitis (GETSBI study)

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ABSTRACT

Introduction Obtaining level 1 evidence on efficacy of glycosaminoglycan (GAG) therapy is difficult, due to low incidence of bladder pain syndrome/interstitial cystitis (BPS/IC) and heterogeneous symptoms experienced by patients with BPS/IC. Currently, because of a lack of high-grade evidence, the recommendation for applying GAG therapy in most guidelines is 'low grade'. An aggregated N-of-1 trial is a multicrossover design that yields similar level 1 evidence as a traditional randomised controlled trial (RCT), while requiring far less patients. The goal of this study is to investigate the efficacy of intravesical GAG therapy (Ialuril) for patients with BPS/IC with Hunner lesions using a dual RCT and aggregated N-of-1 trial design to obtain level 1 evidence.

Methods and analysis The GETSBI study is a double-blind, multidesign multicentre randomised placebo-controlled study to assess the short-term and long-term efficacy of hyaluronic acid (1.6%) + chondroitin sulfate (2%) therapy (Ialuril Prefill, IBSA, Goodlife) in patients with symptomatic BPS/IC with Hunner lesions. It starts as a standard RCT (n=80), but continues as an aggregated N-of-1 trial. There are three parallel arms, receiving blinded treatment for three periods (1 x/week for 6 weeks, ratio placebo to intervention in periods of 2:1). Followed by an open prospective part for the long-term efficacy. The primary study outcome is the maximum bladder pain experienced in the last 3 days measured using the visual analogue pain scale (0–10).

This study is a collaboration with the Dutch government and will deliver evidence for the decision to reimburse the therapy. Furthermore, this multidesign study will allow us to compare the two main methods to evaluate applicability for future study designs for BPS/IC research.

Ethics and dissemination Ethical approval was given by METC Oost-Nederland, file number: 2020-7265, NL-number: NL76290.091.20. Findings from this study will be disseminated via publication, reports and conference presentations.

Trial registration number ClinicalTrials.gov identifier (NCT number): NCT05518864.

STRENGTHS AND LIMITATIONS OF THIS STUDY

By combining the classic randomised controlled trial with an aggregated N-of-1 trial methodology, the study is suitable for group comparison and for within-comparison. For a rare disease with a heterogeneous symptom profile, such as bladder pain syndrome/interstitial cystitis (BPS/IC), this is beneficial.

The study delivers level 1 evidence according to the Oxford CEBM Levels of Evidence.

The aggregated N-of-1 trial is a less established research design.

In the cross-over part in the study there are potential carry-over effects, therefore appropriate washout periods have been incorporated in the study protocol.

An aggregated N-of-1 trial methodology is only possible in chronic disease and non-curative therapies, which is the case for BPS/IC.

INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a symptom-based diagnosis, based on exclusion of other identifiable diseases. It has multiple subtypes defined by the International Society for the Study of Bladder Pain Syndrome (ESSIC). The most severely affected subgroup has disease-specific inflammatory lesions, called Hunner lesions and is classified as ESSIC subtype 3 (BPS/IC HL+). Hunner lesions can be identified and regularly followed up with urethrocystoscopy according to the European EAU guidelines for routine practice. This subtype accounts for approximately 10%–20% of all patients with BPS and is therefore a rare subtype of an already rare disease. Current trends show that the Hunner lesion subtype could be a disease entity on its own.
Aetiology of BPS/IC is unknown. Pathological characteristics include influx of immune cells in the bladder wall and an increased urothelial permeability because of a damaged urothelial layer and a disruption of protective glycosaminoglycans (GAGs) on the bladder wall lumen. Repair of this barrier by exogenous replenishment of GAGs has been a key treatment option for BPS/IC for many years.

Investigating (potential) treatments for BPS/IC is difficult. Randomised controlled trials (RCT) to evaluate GAG therapy have been tried, but many have failed due to heterogeneity of BPS/IC (no subtyping was used) and failure to include sufficient patient numbers for a powered result. In 2015, the reimbursement for GAG therapy was cancelled in the Netherlands due to this lack of level 1 evidence.

Obtaining level 1 evidence is traditionally performed with a double-blinded RCT. Government bodies often rely on this methodology to decide whether to reimburse a therapy. Successfully performing a double-blinded RCT in a rare disease with heterogenous symptoms is challenging due to large sample sizes needed and often the study is not representative of the real-life situation when patients have subjective symptoms like pain or when patients have mixed symptoms. The N-of-1 trial methodology is based on the concept that the most ideal control for evaluating efficacy is when both treatment and placebo are evaluated in the individual patient. Because of this, N-of-1 trial methodology is limited to chronic non-curable diseases/symptoms and their treatments (treatment must be continued over time to supress the symptom or the disease). Results of individual N-of-1 trials in a group of patients with a similar disease can be combined to obtain level 1 evidence for this group. The reliability of this efficacy result goes two-ways: the further this group is stratified, the more representative the efficacy results are for this group. The more the group represents the clinical practise target group, the more it can help to identify potential non-responding and responding subgroups.

Because treatment and placebo are evaluated in a single patient, a study needs far less patients (half or even less depending on evaluation cycles) for adequate power. So far, no aggregated N-of-1 trial has been directly compared with a traditional RCT.

The goal of this study is to investigate the efficacy of intravesical GAG therapy with hyaluronic acid 1.6% + chondroitin sulfate 2% (Ialuril, Prefill, IBSA, Goodlife) for patients with BPS/IC H+ using a research design that is in accordance with a level 1 evidence as defined by the Oxford CEBM evidence grading table.

This study was initiated after discussions between the Dutch Urology Association (NVU) and the Dutch Health-care Insurance Board (ZIN). It will deliver evidence for the decision whether GAG therapy shall be re-reimbursement within the Netherlands.

METHODS AND ANALYSIS

The GETSBI study is a double-blind multideign multicentre randomised placebo-controlled trial to assess the short-term and long-term efficacy of GAG therapy with hyaluronic acid 1.6% + chondroitin sulfate 2% (Ialuril Prefill, IBSA, Goodlife) in patients with BPS/IC H+.

For the short-term, as shown in Figure 1, the study protocol is primarily based on a standard RCT, but continues as an aggregated N-of-1 trial. The outcome of the RCT design is the primary design for evaluation.

![Trial Flow Chart: Standard RCT combined with Aggregated N-of-1 trial](http://bmjopen.bmj.com/)

**Figure 1** Trial flowchart. The patients will be randomised in one of the three parallel arms, receiving blinded treatment for three periods, consisting of 1 ×/week bladder instillation for 6 weeks. The ratio of intervention to placebo periods is 2:1. In between treatments there are wash-out periods for 4 weeks. RCT, randomised controlled trial.
with the aggregated N-of-1 design as a backup in case the inclusion numbers are not met for the RCT design.

For the long-term, the study thereafter continues with an open prospective part evaluating the long-term efficacy of GAG therapy by 1×/4 weeks Ialuril instillation for 6 months. The total follow-up of the study is 54 weeks.

The study is performed at eight sites during two years of recruitment. Eighty patients need to be included. The inclusion criteria are adult (>18 years) patients with symptomatic BPS/IC with Hunner lesions on a cystoscopy in the previous 3 months with a maximum visual analogue scale (VAS) bladder pain score ≥4 on a scale of 0–10 during the last 3 days. The following exclusion criteria are maintained: (1) Pain, discomfort in pelvic region of inflammatory bladder conditions due to any other causes based on patients’ medical history and interview (ie, bladder pathologies and instillations with irritative agents, such as intravesical chemotherapy). There are exceptions for irritable bowel syndrome, hypertonic pelvic floor and urinary tract infections fewer than three per year. These are noted by ESSIC as a confusible diseases; (2) had a urinary tract infection <6 weeks; (3) received bladder instillations for BPS <3 months; (4) received intradetrusor botulinum toxin injections <12 months; (5) received transurethral coagulation/ablation therapy of Hunner lesions <12 months, except for patients who have objectively Hunner lesions recurrence on cystoscopy after coagulation/ablation therapy after at least 3 months postintervention; (6) started a new treatment for (chronic) pain or urinary tract infections in the last month (after 1 month stable use they can be included); (7) unable (also legal) to give informed consent; and (8) allergy/sensibilisations for Hypromellose (this will be tested by applying one drop in one eye). See figure 2 for inclusion flowchart.

The primary objective is the maximum VAS bladder pain score in the last 3 days on a scale of 0–10.

Secondary outcome measurements are: (1) average VAS bladder pain score in the last 3 days on a scale of 0–10; (2) 7-point Global Response Assessment (GRA) scale; (3) VAS-dominant symptom burden score (0–10) (for two most dominant symptoms); (4) voiding urgency as single item from the OS ICSI/PI questionnaire (5-point Likert Scale); (5) voiding frequency as single item from the OS ICSI/PI questionnaire (5-point Likert Scale); (6) O’Leary

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**Figure 2** Flowchart for inclusion. Criteria for inclusion/exclusion and randomisation in three parallel study arms. BPS/IC, bladder pain syndrome/interstitial cystitis; RCT, randomised controlled trial; VAS, visual analogue scale.
Sant Interstitial Cystitis Symptom and Problem Index (OS ICSI/PI); (7) patient-reported outcome (PRO) measurement short form. This includes documentation-specific burden by therapy and start/stop of other BPS treatment; (8) 2×24 hour voiding diary; (9) EQ-5D 5 L Quality of Life questionnaire; (10) urine sediment for screening bacterial UTI; (11) PRO measurement extended version. This includes adverse events reporting and documentation of start/stop of other BPS treatments; (12) cost-effectiveness parameters derived from the Medical Consumption Questionnaire (iMCQ) and Productivity Cost Questionnaire (iPCQ) and finally (13) urethrocystoscopically evaluated parameters: number of Hunner Lesions, estimated % of inflammation of bladder wall (VAS scale 0%–100%) and overall assessment of degree of bladder inflammation (5-point Likert scale). They are measured at time points: week 0, week 8 and week 28. The cystoscopy parameters are secondary outcome measurements, where the (1) change in estimated percentage of inflammation of the bladder wall (area covered by HL) and (2) change in grade of inflammation will be independently evaluated. Moreover, also the correlations between these two secondary outcome measurements will be investigated. All questionnaires are in Dutch.

**Efficacy and statistical analysis**

Because of the heterogeneity of symptoms in patients, efficacy of GAG therapy for BPS/IC with Hunner lesions is defined by three possibilities: (1) an improvement of 2 points on the VAS pain score, or (2) an improvement of 2 points on the VAS score on the most dominant symptom that is reported by individual patient, or (3) an improvement of ≥5 on a 7-point GRA scale. These are parameters used in literature as primary outcome measures for success of treatment. The improvement of 2 points on the VAS pain score and the most dominant symptom was established by an interview with a patient panel, to consider the heterogeneous symptoms in patient with BPS/IC. The GRA scale has been previously used as primary outcome measure in different RCTs for BPS/IC treatments and gives a patient-reported overall assessment of treatment satisfaction.

Analysis of covariances will be used for the VAS pain score as primary outcome measurement, with baseline as covariate. For the aggregated-N-of-I trial hierarchical Bayesians modelling is used for statistical analysis. All patients who completed at least one treatment and one placebo period will be included within the aggregated analysis, with inclusion of all available data.

**Power calculation**

For power calculations, data from Cervigni et al and Nickel et al study were used. These studies resemble our study protocol most regarding the investigational product (hyaluronic acid + chondroitin sulfate or chondroitin sulfate alone), the primary outcome parameters (VAS pain) and RCT design with relative high numbers of inclusion (110 and 98 patients, respectively). Both studies included all BPS/IC subtypes. Cervigni et al used the same HA-CS instillation that is used in this study and showed a treatment effect of approximately −4 on a VAS pain scale (0–10) in comparison with unblinded Dimethylsulfoxide (DMSO) instillations. The Nickel et al study (placebo controlled) showed a placebo effect of approximately −2 on VAS pain scale (0–10). We calculated a SD of 2.62 from the Cervigni et al study. We used a two-sided test and an alpha of 0.05. Using these estimates for the power calculations (>80%), we would require 58 patients in total to detect a significant difference with placebo. The Nickel et al and Cervigni et al studies reported a drop-out ratio between 17% and 25% for 11–24 weeks follow-up (25% would be 15 patients in our study). These studies included all BPS subtypes, we only include the Hunner lesion BPS subtype in our study. This latter subgroup has more severe symptoms compared with the other subtypes and have therefore a higher risk of drop-out. We also have a longer follow-up. Therefore, we increased our inclusion with 22 to a total of 80 patients. In summary, the study will be powered (>80%) for a standard RCT (n=80; consist of 58 + 22 to compensate for potential dropouts). For the aggregated-N-of-I trial design, >80% power will be achieved at 28 patients, considering the drop-out numbers, the required sample size was calculated at a total of 38 patients.

**Recruitment and randomization**

The study will be advertised via the Dutch Patient Association for BPS/IC: ICP, by the Dutch Association for Urology (NVU) and participating research centres. The information about the study will be explained and the patient will receive written patient information and will have ample opportunity to ask questions. After this, they can decide to participate and sign the informed consent form. After a patient has been found eligible for inclusion and signed the informed consent, they will be registered in the secure electronic database (Castor EDC software: according to GMC guidelines). Patients will receive a code and key and is then randomised (software generated). After randomisation, local investigator can view the randomisation outcome in Castor EDC. Local investigator coordinates with the local pharmacy department to prepare investigated product and/ or placebo according to the allocated treatment schedule. If needed the local investigator can perform unblinding in collaboration with the sponsor.

We used the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.

**Patient and public involvement**

For this study a stakeholder’s workgroup has been established to discuss the study and progress. One of the parties in the stakeholder workgroup is the Dutch Patient Association for BPS/IC: ‘Interstitiële Cystitis Patiëntenvvereniging’ (ICP).

**CONSIDERATIONS METHODOLOGY**

Bladder pain syndrome is a symptom-based diagnosis, based on exclusion of other identifiable diseases. It has
multiple subtypes defined by the International Society for the Study of Bladder Pain Syndrome (ESSIC). Subtype 3 is characterised by Hunner lesions. BPS/IC is an orphan disease recognised within the European Research Network for rare diseases. As a rare disease, it has a low incidence and prevalence. Consequently, this applies even more if only subtype 3 with Hunner lesions is considered. Therefore, the number of patients to be included per study design strongly influence the feasibility of the study to recruit enough patients. Previous RCTs failed to show efficacy of GAG therapy in patients with BPS/IC, but these studies did not stratify according to inflammatory and non-inflammatory subtypes (no cystoscopy performed). With inclusion of multiple subtypes, there has been a lot of debate whether these studies had an adequate study design. Therefore, in collusion, and as a requirement of the Dutch government for objective measurements, we decided to only include patients with BPS/IC with Hunner lesions to specify and make the study population more homogenous. Therefore, the addition of the aggregated N-of-1 trial is important as a back-up when inclusions do not meet the power according to the RCT. This study protocol allows for: (1) double blinding, (2) equality between participating patients receiving similar amounts of treatment and placebo and (3) the ability to give each participating patient an individual efficacy result at the end of the study.

The traditional RCT has upsides and downsides. Upsides of a standard RCT are the acceptance as the gold standard in clinical research and the use of randomisation, double blinding and placebo-groups for evaluation. It is therefore very suitable to evaluate therapy effects that apply to a group of comparable patients (between-subject comparison). Also, government bodies mostly rely on the traditional RCT for their decision to reimburse a treatment as is the case for this government supported trial. Downfalls of relying on evidence from traditional RCTs for reimbursement or guideline advice are first seen in obtaining evidence and the reimbursed healthcare in rare disease. Moreover, the traditional RCT is also often not set-up for being representative for real-life clinical practice because of the between-subject comparison limitations. To make study patients comparable to each other, strict inclusion/exclusion criteria are often implemented in the study design. This often leaves out the patients with comorbidities, such as elderly patients who are part of the target population for the investigated treatment.

No direct comparison has been performed between a traditional RCT and an aggregated N-of-1 trial. This trial was therefore set-up to directly compare both study designs without compromising on study outcome measures, study quality and patient burden. It even allows for a direct comparison with a single-crossover RCT design. This will be done by actively comparing/evaluating outcome measurements of the study. This study is double blind with appropriate wash-out periods between treatment periods to minimise possible wash-over bias. The study models will be compared on efficacy (significance) level and on correlation level. The primary and secondary outcomes will be evaluated in average changes (with SD) between the models.

Ethics and dissemination
The GETSBI study will be conducted according to the principles of the Declaration of Helsinki (seventh version, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Ethical approval was given by METC Oost-Nederland, file number: 2020-7265, NL-number: NL76290.091.20. The study will be advertised via the Dutch Patient Association for BPS/IC: ICP, by the Dutch Association for Urology (NVU) and participating research centres. The information about the study will be explained and the patient will receive written patient information and will have ample opportunity to ask questions. After this, they can decide to participate and sign the informed consent form. Benefits for participating in this study are direct reimbursement for the treatment (that is currently not reimbursed) for the duration of the study plus afterwards in the time being the government makes the final decision on reimbursement. Risks are the 6 weeks within the 3.5-month evaluation in which patients get placebo treatment. Considering the duration that patients do get active treatment, this is acceptable in relation to the burden. Therapies are known to be safe with no serious adverse events in previous studies.

Results will be presented at scientific meetings and published in international peer-reviewed journals.

Implementing an RCT with a aggregated N-of-trial design in one study protocol allows not only to determine the efficacy and cost-effectiveness of GAG therapy in patients with BPS/IC HL+ as a rare disease, but also to directly compare the three trial methodologies to obtain level 1 evidence (standard RCT, aggregated N-of-1 trial and single-crossover RCT design), without compromising the scientific value of either of the methods to evaluate applicability for future trial designs for BPS/IC and other chronic diseases.

Collaborators Zorginstituut Nederland.

Contributors DJ initiated this study in collaboration with the government. DJ, FM, CvG and JH all contributed to the design of the study. CvG has written this manuscript. CB, DJ, FM and JH reviewed the manuscript. All authors read and approved the final manuscript.

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Competing interests There is an in-kind contribution of Goodlife Pharma BV to this study.

Patient and public involvement Patients and/or the public were involved in the design, conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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