Nye metoder: Innspill til metoder (forslag/metodevarsler/oppdrag)

Alle har anledning til å komme med tilleggsopplysninger til en metode som er foreslått for nasjonal metodevurdering. Det er ønskelig at innspill kommer inn så tidlig som mulig i prosessen, fortrinnsvis før behandling i Bestillerforum RHF.

Bruk dette skjemaet for å gi innspill til forslag, metodevarsler og oppdrag. På nyemetoder.no vil nye forslag/metodevarsler ha statusen «Forslag mottatt/åpent for innspill» før behandling i Bestillerforum RHF. Utfylt skjema sendes nyemetoder@helse-sorost.no.

NB: **Punkt 1-3 og 11 fylles ut av alle.** Punkt 4-9 fylles ut avhengig av rolle og kjennskap til metoden.

Jeg er klar over at skjemaet vil bli publisert i sin helhet på nyemetoder.no (kryss av): ☒
Har du informasjon du mener ikke kan offentliggjøres, ta kontakt med sekretariatet før innsending.

Jeg har fylt ut punkt 11 nedenfor «Interesser og eventuelle interessekonflikter» (kryss av): ☒

1.Hvilken metode gjelder innspillet?	
Metodens ID nummer*:	ID2022_130
Metodens tittel:	Alfa1-antitrypsin (Prolastina). Vedlikeholdsbehandling for å bremse progresjonen av emfysem hos voksne med dokumentert alvorlig α1-proteinasehemmermangel (f.eks. genotypene PiZZ, PiZ(null), Pi(null,null), PiSZ)

*ID-nummer finner du på metodesiden på nyemetoder.no og har formen ID2020_XXX

2. Opplysninger om den som gir innspill	
Navn	Anki Nygren Book
Eventuell organisasjon/arbeidsplass	Grifols Nordic AB
Kontaktinformasjon (e-post / telefon)	anki.book@grifols.com / +46 705570617

3. Oppsummert innspill til metoden (besvares av alle)
Grifols requests that the efficacy of Prolastina be assessed using the simplified methodology (Forenlet metodevurdering) than the proposed inclusion of a Cost Utility Analysis (CUA). In the case of Prolastina, CUA introduces more complexity and uncertainty in assessing and quantifying Prolastina's impact on utilities or quality of life. While Grifols believes that treatments should improve a patient's quality of life, it acknowledges that clinical situations exist where the quality of life change over time or impact associated with treatment is unusually difficult to measure and quantify, particularly in rare diseases. Mostly this is due to the existence, or lack thereof, of patient specific surveys or instruments with face validity that

capture the appropriate life domains most impacted by the treatment. These survey instruments must be assessed and shown to be psychometrically valid and reliable, able to detect change not conflated with other variables. Generic questionnaires, like the St. George's Respiratory Questionnaire (SGQR), were not developed with rare diseases like Alpha 1 Antitrypsin Deficiency in mind. For example, the response scales associated with the individual questions are likely not sensitive enough to capture clinically meaningful changes associated with lung density improvement. No current questionnaire has been developed nor psychometrically assessed for this task. Given how rare the disease is, conducting clinical trials that use the SGRQ to estimate Utilities would require an unfeasibly large number of patients to enroll and assess.
In sum, it is Grifols' opinion that using a full approach including a CUA has more potential to confound the results than those provided using the simpler methodology. Quantifying the impact on and over time change in Utility or Quality of Life in this patient population, the uncertainty around which life domains are most effected and how much change in lung density is needed before an instrument can detect the impact, is not improved using the more involved CUA methodology.
In addition, the number of patients expected to be treated is limited; Prolastina received regulatory approval in 2008 currently only one patient is on treatment in Norway.

Nærmere informasjon om metoden og innspill til PICO*

*PICO er et verktøy for å formulere presise problemstillinger i metodevurderingsarbeid. PICO er en forkortelse for Population/Problem – Intervention – Comparison – Outcome. PICO brukes til å presisere hvilken populasjon/problem som skal studeres, hvilke(t) tiltak (metode/behandling) som skal vurderes, hvilket tiltak det er naturlig å sammenligne med, og hvilke utfall/endepunkter det er relevant å måle/vurdere. PICO er viktig for planlegging og gjennomføring av en metodevurdering.

4. Kjenner du til om metoden er i bruk i Norge i dag?

To Grifols knowledge, based in sales data, it is believed that one patient is currently treated with Prolastina in Norway.
The product has been sold in Norway since 2013.

5. Hvilken pasientgruppe i den norske spesialisthelsetjenesten er metoden aktuell for? (PICO)

Alpha1-antitrypsin (AAT) deficiency (AATD) is an inherited disease that causes the production of defective AAT and low circulating blood levels of functioning AAT. This results, most commonly, in an increased susceptibility to pulmonary emphysema and liver cirrhosis. Rarer associations are necrotizing panniculitis and granulomatosis with polyangiitis while glomerulonephritis, inflammatory bowel disease and vascular aneurysm are possible associations.

Prolastina is indicated for augmentation therapy in subjects with documented severe alpha1-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi (null,null) and PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV1) predicted,

impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency.

Literature states that in Norway the Pi*ZZ prevalence (mean) is 1 per 2,929 and using the Norwegian population this would result in (95% CI): 1,798 (1,321–2,442) of Pi*ZZ individuals [1]. However, only a small fraction of these patients is expected to be eligible for treatment. In the recent assessment of Prolastina in Denmark the Danish medicines council approximated that around 80 patients were estimated to be eligible for treatment in Denmark. If the same proportionality between number of Pi*ZZ genotypes and patients eligible for treatment is observed in Norway, approximately 35 patients eligible for treatment is expected. There are however large uncertainties is this estimation considering that even with Prolastina approved in Norway since 2008, there is currently only one patient on treatment in Norway.

6. Er du kjent med behandlingsalternativer til denne metoden og hvordan disse fungerer for pasientgruppen i dag? (PICO)

There are two AAT drugs available on the Norwegian market – Prolastina and Respreeza.

There are no national treatment guidelines identified for AATD in Norway. Other treatment options for AATD mentioned in treatment guidelines in the Nordic countries are general and will not impact the development of emphysema but only to prevent deterioration and include smoking cessation, minimizing exposure to environmental hazards, daily exercise to stabilize the disease and utilize the lung capacity as well as COPD medication. In the case of liver disease, treatment recommendations follow those of other chronic liver diseases. Influenza, pneumococcal and hepatitis A and B vaccines are recommended for AAT-deficiency patients. If lung or liver damage is particularly severe, transplantation may be necessary. Only a liver transplantation can solve the underlying cause of the disease.

Worldwide, over the last few decades, many patients with emphysema due to AAT deficiency have been treated with augmentation therapy. The purpose of augmentation therapy is to replace the deficiency in AAT protein and reduce the imbalance in antiproteinase-protease which leads to destruction of the lung tissue. Importantly, augmentation therapy is the only treatment available for patients with AAT deficiency that has been shown to have clinical benefits, such as slowing of the rate of lung density and lung function decline, which are likely to translate to improvements in survival.

7. Har du innspill til hva som vil være viktig for pasienter som er aktuelle for behandling med metoden? (PICO)

Currently, COPD-like symptoms due to progressing emphysema in patients with severe AATD are treated in accordance with current COPD guidelines. The objection to this treatment is that it does not inhibit disease progression - progression of emphysema measured by lung

density - and is purely symptomatic, aimed, for example, at reducing shortness of breath. Augmentation therapy, on the other hand, does combat the cause of AATD by inhibiting disease progression.

Augmentation therapy seems to offer the most benefit in a select group of AATD patients: in nonsmokers or ex-smokers with an alpha$_1$ -antitrypsin (AAT) serum level < 50 mg/dl (11 µmol/l) and with moderate to severe obstruction (FEV_1 between 30-65% of the predicted value) or with a rapid decline in FEV_1 [2, 3].

Augmentation therapy significantly reduces lung density loss - demonstrated via CT scans - which is the most specific and sensitive measure of inhibition of emphysema. Several studies have demonstrated this [4-7][4-7]. Although within the relatively short follow-up period in clinical randomized trials - 2 to 2.5 years - there is no evidence that reduction of lung density loss has an effect on patient endpoints such as mortality and functioning, ~~some~~ observational studies have shown a significant correlation between lung density loss and FEV_1 /FVC, 'efficacy' measures, diffusion capacity (D_{LCO}), quality of life measured by SGRQ, rate of exacerbations and mortality [8, 9].

Furthermore, a dose-effect relationship has emerged in clinical trials, strongly suggesting a disease-modifying effect of augmentation therapy with AAT [4]. There is also evidence that augmentation therapy can reduce the severity of exacerbations - measured by the number of hospitalizations [6]. Furthermore, augmentation therapy has been proven in observational studies to reduce mortality [10, 11] and inhibit the decrease in FEV_1 in AATD [10, 12, 13].

The currently ongoing **S**tudy of **P**rol**A**stin-c **R**andomized **T**herapy with **A**lpha-1 augmentation (SPARTA is a randomized, placebo-controlled trial assessing the efficacy and safety of two separate doses of Prolastin-C (60 and 120 mg/kg) administered weekly over 3 years in patients aged 18-70 years with a diagnosis of AATD and clinical evidence of pulmonary emphysema. The primary measure of efficacy (change from baseline whole-lung 15th percentile lung density [PD15]) will be determined by CT lung densitometry measured at total lung capacity. Secondary efficacy variables will be the evaluation of severe chronic obstructive pulmonary disease exacerbations, as defined by American Thoracic Society/European Respiratory Society criteria, and PD15 of the basal lung region using CT densitometry[14].

In comparison with previous clinical trials investigating the treatment of patients with AATD, the SPARTA trial is placebo-controlled and incorporates two doses of Prolastin-C administered weekly (60 mg/kg or 120 mg/kg). These two dose regimens of Prolastin-C will be administered to enrolled patients for a duration of three years, which exceeds by at least one year the study periods used in previous trials examining the effects of alpha1-PI administration. Furthermore, the established outcome assessments of pulmonary function based on lung architecture will be evaluated by a CT scan at total lung capacity as well as a basal CT scan to evaluate the lower lobes of the lung, which are typically affected by AATD-associated emphysema. Pulmonary function will also be assessed by spirometry measures performed at a central laboratory. SPARTA is anticipated to provide much-needed, robust results to demonstrate the efficacy of Prolastin-C augmentation therapy in patients with AATD[14].

8. Spesielt for medisinsk utstyr (besvares av leverandør): CE-merking
NA

9. Spesielt for legemidler (besvares av leverandør): Markedsføringstillatelse (MT)
Prolastina was granted marketing authorization in Norway 2008-06-06

10. Andre kommentarer
Grifols would like to suggest that Prolastina should be assessed in a simplified assessment (Forenklet metodevurdering) summarizing effect, safety and cost. Considering that Prolastina was granted marketing authorization in Norway already in 2008, there is currently only one patient on treatment in Norway, and that there is limited evidence available to be used for developing a cost-utility analysis (CUA) a simplified assessment is more appropriate. A study with the purpose to determine whether health status defined by the St George's Respiratory Questionnaire (SGRQ) could be employed as part of future AATD trials to provide clearer evidence of patient benefit and how the decline of lung physiology influences the SGRQ decline in patients with AATD never treated with antitrypsin augmentation therapy concluded that the patient numbers needed to detect a difference with disease modifying therapies would be prohibitive especially in this rare cause of COPD [15]. The process of developing a CUA for Prolastina vs standard of care in patients with severe alpha 1-proteinase inhibitor deficiency (e. g. genotypes Pi ZZ, Pi Z(null), Pi (null, null) and Pi SZ based on the clinical data demonstrating reduced lung density loss (as measured by CT-scan) will be based on multiple assumptions and extrapolation of long-term effects of the disease modifying treatment. Hence, the results of the cost utility analysis will be associated with substantial uncertainties. Considering the uncertainties, the addition of a CUA, in this particular case, is not expected to contribute to a more informed decision with regards to the cost-effectiveness of treatment as the analysis is, although clinical evidence is robust, expected to be considered "uncertain".

11. Interesser og eventuelle interessekonflikter Beskriv dine relasjoner eller aktiviteter som kan påvirke, påvirkes av eller oppfattes av andre å ha betydning for den videre håndteringen av metoden som det gis innspill på (for eksempel: økonomiske interesser i saken, oppdrag eller andre bindinger).
Anki Nygren Book is the General Manager for Grifols Nordic. Grifols Nordic is responsible for the marketing and sales of Prolastina in the Nordics on behalf of the MAH Grifols Deutschland GmbH.

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