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_099 ID2022_130
Metodens tittel:	Alpha-1 antitrypsin Prolastina and similar product Respreeza augmentation therapy (IV-AAT) for slowing down the progression of emphysema in adults with documented severe α-1 antitrypsin deficiency- AAT (e.g. genotype 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	Prof. Noel G. McElvaney Head of School of Medicine, Department of Medicine, Royal College of Surgeons in Ireland, Medicine, Beaumont Hospital. https://www.rcsi.com/people/profile/gmcelvaney In collaboration with the LHL Alpha-1 working committee in Norway (Kari D. Aasheim, Knut Skaar, Tikki Tank Nielsen)
Eventuell organisasjon/arbeidsplass	Royal College of Surgeons in Ireland LHL Alfa-1
Kontaktinformasjon (e-post / telefon)	Prof. Noel G. McElvaney: gmcelvaney@rcsi.ie LHL Alfa-1: lhl.alfa-1@lhl.no

3. Oppsummert innspill til metoden (besvares av alle)

This input is written by Prof. Noel G. McElvaney in collaboration with the LHL Alpha-1 working committee in Norway. It provides advice for Nye Metoder/Direktoratet for medisinske produkter (DMP) to support the method evaluation of IV-AAT (Prolastina and Respreeza) for emphysema related to severe Alpha-1 antitrypsin deficiency (AATD).

Our advice is based on a retrospective observational study [1] that included one of the largest cohorts of severely deficient AATD individuals to date. Prof. Noel G. McElvaney was the senior author of the paper, and the study findings were presented in the American Journal of Respiratory and Critical Care Medicine, November 2023.

The RAPID [2] and RAPID-OLE [3] studies have demonstrated that IV-AAT slows down lung parenchymal loss, as measured by computed tomography (CT) scan. The objective of the current study was to conduct further investigations on real-world long-time effects of intravenous IV-AAT on pulmonary function and mortality.

The study followed 615 patients from AATD registries in three countries (Ireland, Switzerland, and Austria), in which basic treatment and access to standard medical care was equal, but access to IV-AAT was not. This study - that examined the real-world long-time effects of IV-AAT - demonstrates a clear survival benefit for recipients of IV-AAT,that is largely decoupled from pulmonary function decline. These findings on mortality reduction complement a previous study.[4]

Two distinct patient populations emerged in the study: *lung indexes,* in which AATD was detected due to respiratory symptoms or airflow obstruction on initial spirometry, and *non-lung indexes,* in which AATD was detected due to other reasons, e.g. family screening.

The study demonstrated that FEV1 decline plateaus in middle aged lung index cases, and furthermore that emphysema progression is decoupled from spirometric decline. Only lung indexes with GOLD stage 2 COPD (50% ≤ FEV1 < 80%) showed a significant difference in FEV1 decline. The potential for IV-AAT to show a meaningful effect on lung function decline in individuals who have entered the plateau phase, is therefore unlikely. Our study hence concludes that FEV1 is unsuitable for assessing IV-AAT efficacy, particularly in older symptomatic AATD patients.

When assessing the evidence of Prolastina/Respreeza we caution that the ability to demonstrate effects on spirometric decline in the RAPID studies was hampered by inclusion of lung index cases in their FEV1 decline plateau phase, e.g. above the age of 50. Nye Metoder/DMP should furthermore take into consideration that the RAPID studies were underpowered to detect IV-

[1] FRAUGHEN, Daniel D., et al. Augmentation Therapy for Severe Alpha-1 Antitrypsin Deficiency Improves Survival and Is Decoupled from Spirometric Decline—A Multinational Registry Analysis. *American Journal of Respiratory and Critical Care Medicine*, 2023, 208.9: 964-974.

[2] Chapman KR, Burdon JG, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, et al.; RAPID Trial Study Group. Intravenous augmentation treatment and lung density in severe a1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386: 360–368. 15.

[3] McElvaney NG, Burdon J, Holmes M, Glanville A, Wark PA, Thompson PJ, et al.; RAPID Extension Trial Group. Long-term efficacy and safety of a1 proteinase inhibitor treatment for emphysema caused by severe a1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). Lancet Respir Med 2017;5:51–60

[4] The Alpha-1 Antitrypsin Deficiency Registry Group. Survival and FEV1 decline in individuals with severe deficiency of a1-antitrypsin. Am J Respir Crit Care Med 1998;158:49–59

AAT effects on exacerbations, hospitalizations, and survival. We thus advise Nye Metoder/DMP to regard CT-scan densitometry findings as a sufficient and valid clinical outcome measure for the efficacy of Prolastina and Respreeza IV-AAT.

Generating substantial evidence for IV-AAT is challenging. The disease progression in severely deficient AATD patients and their reactions to IV-AAT is heterogenous; the irreproducibility of DLCO and other clinical endpoints are not applicable for large multicenter studies. We caution that this too has diminished statistical power.

Several countries apply an upper FEV1 cutoff-limit as eligibility criterion for IV-AAT. However, based on our findings, we advise Nye Metoder/DMP to refrain from limiting access to augmentation therapy in individuals with high, or non-declining FEV1. Presence of emphysema as measured by computed tomography (CT) scan, coupled with a severe deficiency (e.g. genotype PiZZ, PiZ(null), Pi(null, null), PiSZ) and other rare genotypes, that significantly lowers the serum level of AAT, should determine eligibility. Treatment guidelines should furthermore recommend IV-AAT therapy to higher spirometric classes, and earlier in the disease progression than current guidelines. This to prevent destruction of lung tissue, lower individual disease burden, and reduce societal expenditure on health care and disability pension.

Nye Metoder/DMP should note that IV-AAT is unable to regenerate lost lung tissue. It will merely slow down the progression of emphysema. Hence improvements on FEV1, exacerbation frequency and other quality of life measurements may be unrealistic in individuals that have developed emphysema and entered a stage of repeated exacerbations and health decline.

We argue that the current evidence suffices in establishing that IV-AAT is effective in slowing down progression of emphysema in severely deficient AATD patients. Considering the positive results of the IV-AAT in the RAPID studies we furthermore argue that it is unethical to initiate new long-term trials of IV-AAT with a placebo arm. The severity of the illness, the highly limited patient population that will need this treatment, and IV-AAT being the only disease modifying drug available for AATD related emphysema, should also be taken into consideration during the method assessment.

The evidence now supports that IV-AAT (Prolastina/Respreeza) should be offered as standard of care in Norway under public health reimbursement, for individuals with emphysema as measured by computed tomography (CT) scan, and severe Alpha-1 antitrypsin deficiency e.g. genotype PiZZ, PiZ (null), Pi (null, null), PiSZ, and other rare variants.

We recommend that Nye Metoder/DMP ensures that Norwegian Alpha-1 patients can access IV-AAT, which is currently available in several other European countries. By doing so Nye Metoder/DMP would also promote equal access to life prolonging care for Alpha-1 patients on a European level.

Please contact Prof. Noel G. McElvaney and confer with the full text research paper of FRAUGHEN et al., (2023) for further details:

FRAUGHEN, Daniel D., et al. Augmentation Therapy for Severe Alpha-1 Antitrypsin Deficiency Improves Survival and Is Decoupled from Spirometric Decline—A Multinational Registry Analysis. *American Journal of Respiratory and Critical Care Medicine*, 2023, 208.9: 964-974.

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?
Er metoden i bruk utenom kliniske studier i dag: Fra hvilket tidspunkt har den vært i bruk: Hvor er eventuelt metoden i bruk:

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

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

7. Har du innspill til hva som vil være viktig for pasienter som er aktuelle for behandling med metoden? (PICO)
Hva kan oppfattes som en fordel for pasienter og brukere med denne metoden sammenlignet med aktuelle alternativer? Hvilke endepunkter/resultater av behandlingen er det aktuelt å måle? Beskriv kortfattet:

8. Spesielt for medisinsk utstyr (besvares av leverandør): CE-merking
Foreligger det CE-merking for bruksområdet som beskrives i metoden? I så fall angi type og tidspunkt:

9. Spesielt for legemidler (besvares av leverandør): Markedsføringstillatelse (MT)
Har legemiddelet MT for indikasjonen som omfattes av metoden? Angi i så fall tidspunkt eller ventet tidspunkt for MT:

10. Andre kommentarer

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).
Beskriv kortfattet: Professor McElvaney received an unlimited research grant from Grifols in conduction with the current study and has previously received a grant from CSL Behring for research in Alpha-1 antitrypsin deficiency. Furthermore, a speaker honorarium and travel expenses for the ERS congress was covered by CSL Behring during the last 36 months. He is involved in a patent for development of a resistant form of AAT in CHO cells and has furthermore received consulting fees from the following advisory boards: Intellia, Vertex, Inhibrx, Takeda, Dicerna, Centessa in the Alpha-1 antitrypsin deficiency area. Two members of the LHL Alpha-1 working committee have severe Alpha-1 deficiency and will benefit from Prolastina/Respreeza. One of the committee members participated at a CSL Behring Nordic summit on request of Alpha-1 Denmark in 2022, to share a patient story, receiving a fee of 5000 NOK. Two participants in the working committee attended a Nordic Apha-1 patient organization board summit in 2023, and one participated in a 2024 workshop. Their participation was sponsored by Alpha-1 Denmark. Alpha-1 Denmark received CSL Behring grants to conduct the summit/workshop. The working committee would like to emphasize that we are not in a position of loyalty towards producers of IV-AAT. In the interest of our patient community, we welcome all research on Alpha-1 deficiency, and we continuously engage in dialogue with a variety of pharmaceutical companies who develop and trial drugs to treat Alpha-1 antitrypsin deficiency.