Supplementary Figure S3. Tracking confounders when Scalp Coverage Scoring is employed during longitudinal studies.

The fundamental question addressed was whether fluctuations in Scalp Coverage Scoring (SCS), representing clinically perceived coverage, consistently mirror changes in hair productivity over time. Clinicians need to understand when SCS is applicable and become aware of potential confounders, particularly when interpreting the effectiveness of drug treatments. Among the confounders, we identified abrupt changes in hair cycling and modifications in hairstyle and length as significant factors that can disrupt the translation of SCS values into measures of hair productivity through the HMI Abacus. In this study, we tested the robustness of SCS through a total of 396 scores during a longitudinal study involving serial images over a three-year duration of the best responder (1 subject1-3). The baseline covered a 1 year pre-study period with 3 imaging sessions without any drug intake or drug application (shown in FigureS3 panel a; 3 images top left).

There were 132 SCS baseline data computed from triplicate scorings by the principal investigator and a single scoring session by the pool of trained observers.

The follow-up on treatment comprised 6 global images covering a total 24 months (264 SCS Scores). The interested reader will find a detailed explanation of hair length as a confounder for SCS-TTTC correlations by consulting the original set of global images and comments in Figure 10 in a previous paper1). In order to prevent time-related fluctuations of SCS on the 9 global images displayed according to time (Figure S3a) were randomised. The baseline SCS fluctuations (panels a1. Baseline SCS 0) were grouped as time 0 (Figure S3b shows average SCS on global views recorded at the recruitment phase of volunteers (year-1) and visits 1 month before (m-1) and on the start of drug trial (m0). According to the study protocol, there was a first phase with 3-monthly visits (Figure S3a2 m1, m2 and m3) on combined treatment with oral finasteride (Propecia™; 1mg/day) and topical minoxidil 5% lotion (1ml once a day; Alostil™) ending at 2 years after initiation of oral drug treatment (imaging at time-points m3, m6, m12 and m24 show results without topical lotion; Figure S3a3).

There were 2 confounders: a styling effect with increased average SCS at m1 without statistically significant changes of productivity and increased SCS at month 6 when productivity was reduced after weaning off minoxidil with hair being retained in telogen (shift from anagen to telogen between m3 to m6). A new cycle was initiated after exogen, and it took a while (after m12) for SCS to recover perfectly. This is associated with re-cycling, as shown in panels a.C under the continuous oral intake of finasteride as a monotherapy (Figure S3b; raised SCS from m12 to m24). Overall, the correlation between SCS by 8 duly trained dermatologists who completed the session vs the principal investigator (Figure S3c; r2=0.83) supports the HMI approach. This outcome is contingent upon maintaining a standardized hairstyle. It corroborates our prior findings from a six-month randomized, placebo-controlled clinical trial involving a topical anti-androgen across three centers (two in France and two in Belgium) involving 200 males with patterned hair loss. This trial, which included 4,800 scorings both in vivo and via computer screen images and a phototrichogram study (unpublished data**)** demonstrated that in the absence of statistically significant changes in hair productivity, there were no clinically perceived changes in SCS. In summary, although SCS may fluctuate due to sudden changes in hair cycling and hair length or style, the combination of scalp hair productivity with SCS could be considered a strong candidate for the gold standard to objectively monitor and evaluate efficacy during long-term clinical trials.

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