Digital technologies to support the delivery of pulmonary rehabilitation for adults with chronic obstructive pulmonary disease [GID-HTE10019]

Addendum #3

Response to requests post-draft guidance

February, 2024

Produced by

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Declared competing interests of the authors

None

Rider on responsibility for document

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

This addendum is linked to ERG report

Barnish et al.Digital technologies to support the delivery of pulmonary rehabilitation for adults with chronic obstructive pulmonary disease [GID-HTE10019]. EAG report. Peninsula Technology Assessment Group (PenTAG), 2023.

1. INTRODUCTION

The purpose of this addendum is to address a request to respond to further stakeholder comments from NICE, after the publication of the draft guidance.

The EAG provides the following responses to points which were highlighted by NICE in the consultation comments spreadsheet (these were from Wellinks in row 17, and from Aseptika in row 26).

This addendum provides the EAG's clinical and economic commentary on the newly available evidence cited by Wellinks and Aseptika. This document complements, and adds to, the EAG responses provided in addendum 2.

Please note that the scope of this addendum only includes review of the additional documents provided by the two companies Wellinks and Aseptika. It does not include a new search to identify and critique all potentially available new evidence across interventions.

The two new documents are an in-press manuscript[1] on an interventional study for Wellinks and an unpublished manuscript[2] for Active+me REMOTE. If these had been available at the time, these would have met inclusion criteria to feature in the EAG report. As agreed with NICE, the EAG presents a commentary on this additional evidence as an addendum, so that the NICE Committee can consider the next steps for the appraisal.

2. COMMENTARY ON THE ASPIRE STUDY

2.1. Background

Commentary on the draft guidance from Wellinks included the following:

> *"Wellinks is appreciative of the committee's efforts to identify and review the evidence base for these technologies.*
>
> *"We would like to draw the committee's attention to the results from the ASPIRE study, which has been recently reviewed and accepted by peer reviewers and is currently in pre-print with JMIR here: https://preprints.jmir.org/preprint/47555/accepted"*

2.2. EAG commentary on the clinical evidence

The new document, Pierz et al. (2023),[1] reports the results of a 24-week 'interventional research study' on Wellinks. This is an in-press manuscript available on the journal's website. The study characteristics are presented below as Table 1.

The EAG considered this study to address a research question relevant to the decision problem. The study would have been considered prioritised evidence for Wellinks, as it is an interventional study, albeit one that used sequential rather than random allocation, and had an internal (different amount of coaching provision for Wellinks) rather than external control arm. It was conducted within an adult COPD population in the United States, although only people with smartphone and internet access were eligible to participate. There may be differences between the UK and American contexts, although generally the evidence would be considered to generalise well to a UK context. The EAG considered the sequential rather than random allocation to be a substantial limitation, as it may give rise to selection bias and confounding.

Table 1. Study characteristics for Pierz et al.

Country	Population	Design	Sample size	Intervention	Comparator	Outcomes
United States	Adults with COPD who had phone and internet access, owned a smartphone and were not currently participating in pulmonary rehabilitation	24-week interventional study with sequential assignment (arms diverge at 12 weeks at which stage participants are told their assignment)	141 completed onboarding; 119 remained engaged	Wellinks COPD solution, with health coaching in one-to-one 30-minute virtual sessions every other week for the first 12 weeks, then text messages or up to three 15-minute check-in sessions in total across the next 12 weeks	Wellinks COPD solution, with health coaching in one-to-one 30-minute virtual sessions every other week for the first 12 weeks, and no access to coaching sessions for the next 12 weeks	Compliance with protocol-recommended device utilisation, compliance with coaching session attendance, participant ratings of components of Wellinks COPD Solution, quality of life (published correlations with COPD Self-Efficacy Scale and Modified Medical Research Council Dyspnoea Scale), healthcare resource utilisation, pulmonary function using at-home devices to measure FEV_1, PEF and SpO2.

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV, forced expiratory volume; PEF, peak expiratory flow; SpO2, oxygen saturation

Demographic features were well-balanced between study arms. Study participants had a mean age of 70 (range 48-88) and 56% were female. The study sample was 91% white ethnicity. The majority of participants were former (84%) or current (9%) smokers, as may be expected for a COPD population. Most participants (82%) reported being under the care of a pulmonologist for their COPD, 40% reported primary care physician involvement in their care, and three-quarters (74%) reported having COPD for at least five years prior to study enrollment. Participants typically had moderate (51%) or severe (40%) COPD severity and more than half (58%) did not have an exercise plan at study enrollment.

Participant engagement was good during the initial 12-week period (84% of participants attended all coaching sessions) but declined during the following 12 weeks (only 51% of those in the arm with three 15-minute check-in sessions attended them all). Similarly, spirometer compliance declined from 82% in week one to 42% at week 12 and 9% at week 24. Pulse oximeter compliance declined from 89% in week one to 43% at week 12 and 9% at week 24. Compliance with the Wellinks app itself also declined over the study period from 94% in week one to 51% at week 12 and 23% at week 24. The 12-week survey was completed by 79% of participants, while the 24 weeks survey was completed by 74% of participants allocated to receive brief check-in sessions (intervention) but only 35% of participants allocated to receive no further coaching follow-up (control).

At study completion, 93% of participants in the intervention arm strongly agreed or agreed that *“using the Wellinks Solution has helped me to learn more about my COPD”*, compared to 69% of participants in the control arm. The Net Promoter Score at week 24 (i.e. how likely responders were likely to recommend Wellinks to others with COPD) was higher in the intervention arm (+64) than the control arm (+55). However, the results for the control arm should be interpreted cautiously considering the low response rate.

Clinical outcomes are shown below in Table 2. While scores suggest an improvement in self-efficacy over time on Wellinks, this was not found for dyspnoea. The study assessed whether follow-up beyond 12 weeks is beneficial, so could not directly assess the benefit of Wellinks versus no intervention. It was not powered as an equivalence study. It should be noted that allocation was not randomised and this could lead to selection bias and confounding.

Table 2. Clinical outcomes for Pierz et al.

	Baseline	12 weeks	24 weeks
COPD Self-Efficacy Scale Total Score; Mean (SD)	103.9 (28.71)	NR	NR
COPD Self-Efficacy Scale Total Score; LS mean change from baseline (SE)	NA	11.1 (3.10)***	23.6 (4.81)***
COPD Self-Efficacy Scale Total Score; LS mean change from 12 weeks (SE)	NA	NA	Intervention 8.6 (4.04)* Control 10.6 (4.33)*
Modified Medical Research Council Dyspnoea Scale; Mean (SD)	2.0 (1.26)	NR	NR
Modified Medical Research Council Dyspnoea Scale; Responder status (%)	NA	Improved 32% No change 56% Worsened 13%	Improved 35% No change 47% Worsened 18%

Abbreviations: NA, not applicable, NR, not reported. * = p<0.05, ** = p<0.01, *** = p<0.001.

Patient satisfaction with Wellinks was generally high, although engagement declined markedly over time on all measures. During the period of exposure to Wellinks, COPD Self-Efficacy Scale scores improved, although the change from 12 to 24 weeks was reported to be greater in the group that did not receive additional coaching input during this period. The company also provided scores for each sub-domain of the scale, which can be found in Pierz et al.[1] Around half of participants experienced no change of category on the Modified Medical Research Council Dyspnoea Scale, although more participants improved than worsened.

There were no adverse events reported by participants during the study period. However, as adverse event data collection relied on spontaneous reporting from participants, it is possible that certain events may not have been reported.

Pulmonary function and pulse oximetry results were not presented by the company. The rationale given was small sample size, in combination with declining utilization of connected data collection devices over the study period. The EAG considered this reasonable, although also noted that, if sufficient data had been available, these measures could have provided useful insight into the objective physiological benefits of treatment.

Detailed results for healthcare resource utilisation were not reported by the company in sufficient detail to be tabulated. It was noted that more than 90% of participants did not report any emergency department visits or hospitalisations before or during the study. Participants most commonly reported either no or only one COPD-related physician visit for the three-month period prior to each measurement timepoint.

2.3. EAG commentary on the economic evidence

Though the Pierz et al. study provided outcomes for COPD self-efficacy scale and MRC Dyspnoea scale as given in Section 2.2, it did not provide any data on exercise capacity measured in terms of walking distance. Also, the Wellinks technology costs were not provided by the manufacturer. Therefore, it was not possible for EAG to include Wellinks in the economic analysis (neither in CCA nor in CEA).

However, the table of disaggregated consequences or effects (Table 9) provided in the original EAG report was updated to include the new data for Wellinks as well as Active +me REMOTE, as provided below (Table 3). Results are reported as mean difference in the change over time between intervention and control, unless otherwise stated.

Please note that though this addendum relates to the new information provided on Wellinks and Active +me REMOTE (see Section 3), for completeness and to facilitate the ease of comparison the whole table with all the technologies from the original EAG report has been presented here.

Table 3. Disaggregated consequences or effects

	Clinitouch vs F2F PR			MyCOPD vs F2F PR			SPACE for COPD vs TAU[a]			Kaia Health vs TAU[b]			Rehab Guru[c]			Active +me REMOTE[x]			Wellinks		
Consequences (disaggregated)	**N (I,C)**	**Diff**	**P**	**N (I,C)**	**Diff**	**P**	**N (I,C)**	**Diff**	**P**	**N (I,C)**	**Diff**	**P**	**N (I,C)**	**Diff**	**P**	**N (I,C)[y]**	**Diff**	**P**	**N (I,C)**	**Diff**	**P**
Exercise capacity																					
6MWT, m	[redacted]	[redacted]	[redacted]	(64, 26)	23.8[d]	0.098							45								
ISWT, m							?<(52, 70)[e]	24.8[f]	NS							69 (59,NR[z])					
EWST, s							?<(52, 70)[g]	40.6[h]	NS												
STST										<(33, 34)[i]	0.390	0.143									
HRQoL																					
EQ-5D-5L, mean difference (%)	[redacted]	[redacted]	[redacted]						NS[j]							69 (0.03, NR[z])					
EQ-5D VAS, mean difference in change	[redacted]	[redacted]	[redacted]						NS[j]							69 (2.0, NR[z])					
SGRQ				(64, 26)	-3.72[k]	0.291															
CRQ (dyspnoea)							?<(52, 70)[l]	0.0[m]	NS	<(33, 34)[n]	0.570	0.033				69 (6.6, NR[z])					
CRQ (total)										<(33, 34)[o]	0.508	0.056									
COPD Self-efficacy scale total score[^^]																			141 (23.6, NR[z])		
Respiratory function																					
CAT[p]	[redacted]	[redacted]	[redacted]	(64, 26)	-1.0[q]	0.373	?(52, 70)[r]	0.511[s]	0.575	<(33, 34)[t]	-0.605	0.024				69 (-2.9, NR[z])					
MRC dyspnoea	[redacted]	[redacted]	[redacted]	(64, 26)	0.03[u]	0.909							-1			69 (-0.5, NR[z])					
MRC dyspnoea responder status at 24 weeks (%)																			No change or improved: 82%		
Adverse events																					
Number of AE events				(64, 26)	3	2	11 (none due to treatment)	7								46 (Serious: 2/46. None due to treatment)					
ED or resulting in Hospitalisation				1.88[v]	1.06[v]	0.82[v]				1.08[w]	1.23[w]	-0.15[w]									
Source(s)	Staffordshire report by Clinitouch[3]			Bourne et al. 2017[4] and hospitalisation data from North et al. 2020[5]			Bourne et al., 2022[6] except Chaplin et al. 2017[7] where stated.			Spielmanns et al. 2023[8]			Rehab Guru poster by Pilsworth et al.[9] & CS			Active +me REMOTE hybrid PR feasibility study[2]			Pierz 2023[1]		

Abbreviations: 6MWT = 6-minute walk test; AE = adverse events; C = comparator; CAT = COPD Assessment Test; CRQ = Chronic Respiratory Disease Questionnaire; CS = company submission; Diff = difference; ED = emergency department; ESWT = endurance shuttle walk test; I = intervention; ISWT = incremental shuttle walk test; m = metres; MRC, Medical Research Council; s = seconds; SGRQ, Saint George's Respiratory Questionnaire; STST = sit-to-stand test

[a] TAU could include PR.

[b] Unknown whether TAU included PR.

[c] No comparative data available for Rehab Guru

[d] Adjusted, ITT population.

[e] Sample sizes for individual outcomes not reported explicitly reported, but primary outcome (CAT) data availability was (52,70), with between 2.6% and 52.3% of data missing for others.

[f] Baseline ISWT and ESWT in control group not reported. Details of statistical tests not reported. Figures shown are difference in metres between intervention and control at 9m

[g] Sample sizes for individual outcomes not reported explicitly reported, but primary outcome (CAT) data availability was (52,70), with between 2.6% and 52.3% of data missing for others.

[h] Baseline ISWT and ESWT in control group not reported. Details of statistical tests not reported. Figures shown are difference in metres between intervention and control at 9m

[i] 60 of 67 patients completed the study but data missingness not reported.

[j] Source: Chaplain 2017. Data not reported, but declared NS

[k] Adjusted, ITT population.

[l] Sample sizes for individual outcomes not reported explicitly reported, but primary outcome (CAT) data availability was (52,70), with between 2.6% and 52.3% of data missing for others.

[m] Difference in change from BL to 9m. 6m figures: 0.0, NS

[n] 60 of 67 patients completed the study but data missingness not reported.

[o] 60 of 67 patients completed the study but data missingness not reported.

[p] As CAT represents the impact of the disease on patient life a negative value in the table represents a decrease in that impact and an improvement in patient health

[q] Adjusted, ITT population

[r] Sample sizes for individual outcomes not reported explicitly reported, but primary outcome (CAT) data availability was (52,70), with between 2.6% and 52.3% of data missing for others.

[s] At 9m FU. 6m mean difference 1.70, p=0.135

[t] 60 of 67 patients completed the study but data missingness not reported.

[u] adjusted, ITT population.

[v] Mean in-patient treated

[w] Mean exacerbations treated

[x] The intervention is Hybrid PR (Centre-PR: two supervised in-person sessions per week for eight weeks in a group setting at a hospital or community site) + Active +me REMOTE app)

[y] Reported values are mean change from baseline for intervention

[z] Not reported in the study

[^^] Mean change from baseline at 24 weeks

2.4. Discussion and implications

The EAG presents here additional results from one interventional study with sequential assignment. In the original EAG report, the available evidence for Wellinks was an eight-week single-arm observational study also conducted in the USA (Gelbman & Reed, 2022).[10] The Gelbman & Reed study provided data on forced expiratory volume and COPD GOLD staging, but all information was provided as a cross-sectional snapshot and did not show whether any improvement in outcomes was associated with exposure to Wellinks. The Pierz et al.[1] study adds to this evidence by presenting data over a 24-week study, showing change over time in outcomes. Furthermore, results were available for a limited range of outcomes, principally participant engagement and satisfaction, COPD Self-Efficacy Scale and Modified Medical Research Council Dyspnoea Scale scores. However, not all outcomes could be presented subdivided by arm, showing whether there was any benefit of coaching input beyond 12 weeks. The available findings were uncertain regarding the potential benefits of exposure to Wellinks.

The Pierz et al.[1] study may in part address some of the evidence gaps highlighted in the original EAG report. Some data are provided to address health-related quality of life. This is likely to move from the red category to the amber category. However, it should be noted that the results are not conclusive, and the measure used is not a direct measure of quality of life, but rather a proxy measure shown to correlate with quality of life instruments. Further information for intervention completion is provided, although this is likely to remain in the amber category due to the marked reduction in engagement over time. Adverse events and hospitalisations may move from the red category to the amber category, although the data provided are limited and subject to potential reporting bias.

In conclusion, one additional interventional study (not an RCT) is provided for Wellinks, to complement the observational study discussed in the original EAG report. The EAG considered that the potential benefits of Wellinks remain uncertain, due to a combination of results being available for few clinical outcome measures and uncertain findings for key outcomes. Further, EAG would like to note that the Pierz et al. 2023 did not assess exercise capacity outcomes measured in terms of walking distance (6MWD or ISWD), which was the outcome considered in the economic analysis. In addition, the cost of technology was also unavailable for Wellinks. Therefore, EAG was unable to consider Wellinks in its updated economic analysis.

3. COMMENTARY ON THE HAREFIELD HOSPITAL STUDY

3.1. Background

Commentary on the draft guidance from Aseptika included the following:

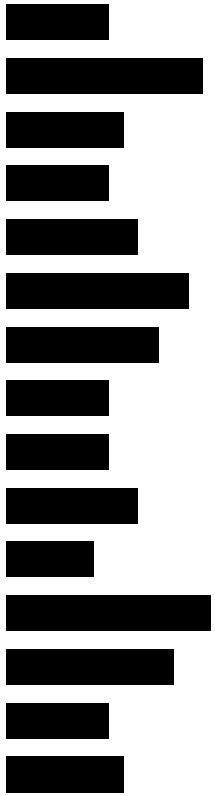
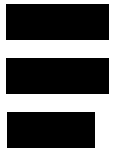
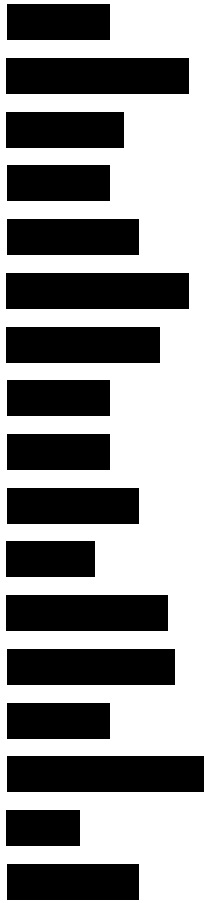
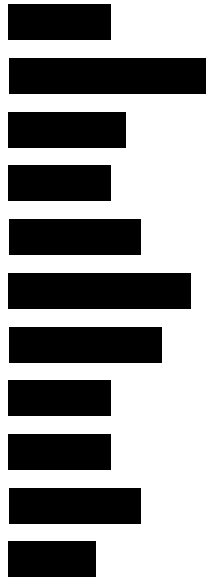
> *"Aseptika can now present the clinical report from Harefield Hospital which indicates better outcomes based on the evaluation criteria, digital technologies used by themselves. This report, prepared independently is attached. Please note the conclusions about the improved performance compared with other digital-only solutions.*
>
> *"We propose that the assessment is paused while these latest data are considered so as to provide patients of with a genuinely choice of solution, and so this EVA based on the latest data. If these data had been available at the start of the EVA, our view is that Active+me REMOTE for PR would have be included in the further research needed group along with myCOPD and SPACE for COPD.*
>
> *"We therefore formally request that these latest data are considered and the publication is delayed until they are incorporated into the report. We had informed NICE that these data would be available in December from the outset."*

3.2. EAG commentary on the clinical evidence

The company present an unpublished report on the Harefield Hospital study.[2] The study characteristics are presented below in Table 4.

The EAG considered this study to address a research question relevant to the decision problem. No prioritised evidence was available for Active+Me REMOTE in the original EAG report. Therefore, the EAG considered that this [redacted] likely be considered prioritised evidence. However, it should be noted that this work has not been peer-reviewed. It was conducted within the United Kingdom in West London and was described as a [redacted] It assessed [redacted]

Table 4. Study characteristics for the Harefield Hospital Study

Country	Population	Design	Sample size	Intervention	Comparator	Outcomes
United Kingdom						

Abbreviations: COPD, chronic obstructive pulmonary disease; PR, pulmonary rehabilitation

At baseline, within the [redacted] group, the mean age was [redacted] and [redacted] of participants were male. Mean Medical Research Council Dyspnoea scale score was [redacted]The sample was on average [redacted]Mean Index of Multiple Deprivation decile was [redacted]. Baseline characteristics are not provided for [redacted], which was considered a limitation. It should be noted that the intervention for Active+me REMOTE was [redacted]options were not considered in the EAG report for other interventions as part of the process to prioritise evidence to deliver a report within the resource constraints of an EVA.

Table 5 shows clinical results for the Harefield Hospital Study. Findings are reported for a [redacted] relevant outcomes and show a [redacted]

However, it was not made clear in the company report whether these change scores were the absolute change [redacted].
This complicates the interpretation of the findings.

Changes in [redacted]for these outcome measures.

Table 5. Results for ACTIVE+me REMOTE from the Harefield Hospital Study

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease

A total of [redacted] adverse events were recorded in the intervention group, of which [redacted] were considered serious requiring hospitalisation. [redacted] of the serious adverse events were considered by the company to be related to the intervention. However, no information was provided about how many of the [redacted] were related to the intervention.

The report supplied by the company says that results from the [redacted] are reported elsewhere but did not signpost the EAG to where this information can be found. Therefore, the EAG could not include the [redacted] in this addendum. It should be noted that this study was not randomised, which could give rise to selection bias and confounding.

In conclusion, the EAG considered that the Harefield Hospital study does show [redacted], although this assessment is complicated by methodological uncertainty about the statistical analysis.

3.3. EAG commentary on the economic evidence

The Active+me REMOTE Harefield hospital study included the change from baseline in terms of incremental shuttle walking distance (while the EAG were not certain if the change scores were vs baseline or vs historical control, the EAG have assumed for the purposes of this economic evaluation that they're against baseline). This is a relevant outcome for the economic analysis, which was previously unavailable. EAG has therefore updated both the reference case CCA and the exploratory CEA (including the CE model) with the exercise capacity outcome for Active+me REMOTE. The EAG note that the cost of Active+me has remained the same since the original report and hence no update was required in terms of its costs.

Please refer to Section 2.3 for the disaggregated consequences or effects from the Harefield hospital study for Active+me REMOTE.

Table 6 below presents the updated cost-consequence balance sheet. It is to be noted that a 59m mean change from baseline was reported in the Harefield study for Active+me REMOTE hybrid PR intervention. Whereas, based on the UK COPD PR audit data (2015) for face-face pulmonary rehabilitation the change from baseline was 63.4m for ISWD, derived as the weighted average of the practice and no practice cohorts.[11] This resulted in a [redacted]m difference in treatment effect between Active +me hybrid PR and face-to-face PR (as per 2015 audit).

Table 6. Cost-consequences balance sheet

	Clinitouch vs F2F PR (UK COPD PR audit)	myCOPD vs F2F PR (UK COPD PR audit)	SPACE for COPD vs F2F PR (UK COPD PR audit)	Rehab Guru vs F2F PR (UK COPD PR audit)	Active +me REMOTE vs F2F PR (UK COPD PR audit)
Difference in treatment effect, 6MWD in m	[redacted]	-14.1	NR	-14.0	[redacted]
Difference in treatment effect, ISWD in m	NR	NR	-18.4	NR	[redacted]
Annual cost savings per participant	[redacted] -£261	[redacted] [redacted] first year[b] [redacted] second year[b]	-£218	-£255	[redacted] [redacted]

Abbreviations: 6MWD, 6-min walking distance; F2F, face-to-face; ISWD, incremental shuttle walking distance; NR = not reported

[a] per participant license fee based on 'legacy' contract

[b] per participant license fee based on pricing model with 10% uptake rate at first year and 20% in the following years

[c] calculated using the mean change from baseline value for Active+me REMOTE hybrid PR

[d] calculated assuming Active+me technology costs did not include the mean number of supervised sessions (i.e. 8.5 as per Harefield hospital study as part of 'hybrid PR')

The annual cost savings per participant was £97 for Active+me REMOTE (calculated as: £335 (total technology cost for Active+me) - £432 (total technology cost for F2F PR)). However, when per participant technology costs were calculated assuming that the mean number of supervised sessions (i.e. 8.5 as per Harefield hospital study) were not included, the savings reduced to [redacted] for Active+me REMOTE. The savings were lower for Active+me, as the license costs were higher compared to other digital technologies. In addition, per participant training costs for patients were incurred, as well as for clinicians.

The cost-effectiveness analysis and the decision analytic framework (or model) used for CEA were also updated to include the ISWD data for Active+me REMOTE. Table 7 presents the key model inputs for the CEA with the per participant technology costs of Active+me included.

Table 8 to

Table 10 present the base case results of the CEA with Active+me REMOTE added. Results are shown for the following outcomes: 1) absolute change from baseline in exercise capacity, measured as walking distance in meters, 2) percentage change from baseline in exercise capacity, measured as walking distance, and 3) unit change from baseline in MCID of exercise capacity, measured as MCID.

The EAG considered that the face-to-face pulmonary rehabilitation data from the UK COPD PR audit are closer to real clinical practice and hence only the results comparing digital technologies to that of UK COPD PR audit have been presented here.

It is to be noted that the range of incremental effects remained the same when including Active+me REMOTE. However, the range of incremental costs changed (-£261 to -£97), with Active+me REMOTE producing the least savings owing to its high per participant technology costs.

Table 7. Model inputs CEA

	Annual per participant costs (£)	Uptake, %	Completion, %	Per participant effects (measured as change in functional exercise capacity)		
				Absolute mean change from baseline (6MWD or ISWD in metres)	% change from baseline	Change from baseline measured as MCID units
Digitally supported pulmonary rehabilitation technologies (considering license fee, staff time and training costs)						
Clinitouch (CT)	[redacted] £170.55[b]	10%[f]	76.6%	[redacted]	[redacted]	[redacted]
myCOPD (MC)	[redacted] (using license fee corresponding to 10% uptake)[e]	10%[f]	62%	44.9[c]	12%	0.831
Rehab Guru	£177	10%[f]	68%	45[c]	18%	0.833
Active +me REMOTE	£334.55[g] [redacted]	10%[f]	NR	[redacted]	[redacted]	[redacted]
SPACE for COPD	£213.29	10%[f]	47%	45[d]	15%	0.947
Face-to-face pulmonary rehabilitation						
F2F PR – 6MWD based on UK COPD PR audit (without exacerbation costs)	£432	85%	71%	59	22%	1.092
F2F PR – ISWD based on UK COPD PR audit (without exacerbation costs)				63.4	31%	1.320

	Annual per participant costs (£)	**Uptake, %**	**Completion, %**	**Per participant effects (measured as change in functional exercise capacity)**		
				Absolute mean change from baseline (6MWD or ISWD in metres)	**% change from baseline**	**Change from baseline measured as MCID units**
F2F PR CT control arm	£272.83	70%	55.63%	[redacted]	[redacted]	[redacted]
F2F PR myCOPD control arm	Assumed same as UK COPD PR audit	95%	72%	28.6	7%	0.530
F2F PR SPACE control arm	Assumed same as UK COPD PR audit	95%	67%	Assumed same as UK COPD PR audit		

Abbreviations: 6MWD, 6-min walking distance; F2F, face-to-face; HCP, health care professional; ISWD, incremental shuttle walk distance; NR, Not reported; PR, pulmonary rehabilitation; UK, United Kingdom.

Note: As F2F arm was not available in the Rehab Guru study, it was assumed to be the same as UK COPD PR audit.

[a] Cost based on confidential per clinical per annum price reported in the company submission.

[b] Cost based on publishable license fee of £26.67.

[c] Clinitouch, Rehab Guru and myCOPD results are expressed as 6MWD.

[d] SPACE for COPD results are expressed as ISWD.

[e] Calculated as: 144+64 (license fee for 10% uptake)

[f] Based on the NHS England data from COPD PRIME tool, proportion who starts PR out of COPD population with MRC3 and above = 59,003/667,040 ~ 9%, rounded up to 10%

[g] Calculated as: Per participant license fee (£89) + training costs for clinician (£41.67) and patient (£60) + staff time costs (£143.88)

[h] Calculated as: Active+me technology costs (£334.55) + PSSRU 2022 community services physiotherapy costs per group session/Number of participants per group assumed to be 12 * Mean number of supervised sessions (8.5) (as per Harefield hospital study) (£92/12*8.5)

Table 8. Cost per change in walking distance – F2F PR UK COPD PR audit

	Costs (per annum per participant)	Effect (Change in walking distance, m)	Digital vs F2F PR		
			Incremental costs	Incremental effect	Cost per ΔWD(m)
Clinitouch (CT)	£170.55	[redacted]	-£261	[redacted]	£2,355
F2F PR	£431.55	59.01	-	-	-
myCOPD (MC)	[redacted]	44.90	[redacted]	-14.11	[redacted]
F2F PR	£431.55	59.01	-	-	-
SPACE for COPD	£213.29	45.00	-£218	-18.38	£12
F2F PR	£431.55	63.38	-	-	-
Rehab Guru	£176.50	45.00	-£255	-14.01	£18
F2F PR	£431.55	59.01	-	-	
Active +me REMOTE	£334.55	[redacted]	-£97	[redacted]	£22
F2F PR	£431.55	63.38	-	-	-

Abbreviations: F2F, Face-to-face; MCID, minimal clinically important difference; PR, Pulmonary rehabilitation; WD, walking distance in meters

MCID reached MCID not reached

Table 9. Cost per unit change in MCID[a] – F2F arm as per UK COPD PR audit

	Costs (per annum per participant)	Effect (change in MCID units)	Digital vs F2F PR		
			Incremental costs	Incremental effect	Cost per unit ΔMCID
Clinitouch (CT)	£170.55	[redacted]	-£261	[redacted]	£127,167
F2F PR	£431.55	1.093	-	-	-
myCOPD (MC)	[redacted]	0.831	[redacted]	-0.261	[redacted]
F2F PR	£431.55	1.093	-	-	-
SPACE for COPD	£213.29	0.947	-£218	-0.387	£564
F2F PR	£431.55	1.334	-	-	-
Rehab Guru	£176.50	0.833	-£255	-0.259	£983
F2F PR	£431.55	1.093	-	-	-
Active +me REMOTE	£334.55	[redacted]	-£97	[redacted]	£1,051
F2F PR	£431.55	1.334	-	-	-

Abbreviations: F2F, Face-to-face; MCID, minimal clinically important difference; PR, Pulmonary rehabilitation; WD, walking distance in meters

[a]1 MCID for 6MWD = 54m and ISWD = 48 m.

MCID reached MCID not reached

Table 10. Cost per % change in walking distance – F2F arm as per UK COPD PR audit

	Costs (per annum per participant)	Effect (% change in walking distance)	Digital vs F2F PR		
			Incremental costs	Incremental effect	Cost per % ΔWD
Clinitouch (CT)	£170.55	[redacted]	-£261	[redacted]	£11,709
F2F PR	£431.55	22%	-	-	-
myCOPD (MC)	[redacted]	12%	[redacted]	-11%	[redacted]
F2F PR	£431.55	22%	-	-	-
SPACE for COPD	£213.29	15%	-£218	-15%	£1,416
F2F PR	£431.55	31%	-	-	-
Rehab Guru	£176.50	18%	-£255	-4%	£5,902
F2F PR	£431.55	22%	-	-	-
Active +me REMOTE	£334.55	[redacted]	-£97	[redacted]	£1,450
F2F PR	£431.55	31%	-	-	-

Abbreviations: F2F, Face-to-face; MCID, minimal clinically important difference; PR, Pulmonary rehabilitation; WD. walking distance in meters

MCID reached MCID not reached

One-way and two-way sensitivity analyses were also performed. Face-to-face pulmonary rehabilitation data from the UK COPD PR audit has been used for all the sensitivity and scenario analysis, as it was found to reflect clinical practice more closely.

Threshold analysis of change from baseline ISWD indicated that when a threshold value of 65m and above was tested, Active+me REMOTE hybrid PR was cost saving and more effective. Below the threshold value of 65m it was still cost saving but less effective compared to F2F PR (based on 2015 audit data), as shown in Table 11. However, these threshold values are subject to uncertainty based on baseline values in the face-to-face arm. This has been explored further in the sensitivity analysis. As shown in

Table **12**, Active+me would be cost saving and more effective if the change from baseline in the face-to-face arm was less than 55m.

One-way sensitivity analysis of uptake rates of the digital technologies was also performed. This indicated that for Active+me the costs savings are not impacted with changing uptake rates (

Table 13), as the per participant costs per the pricing model were not linked to uptake levels of the technology.

Table 11. OWSA – Impact of change in walking distance on cost per ΔWD

	Cost per ΔWD				
Change from baseline WD, m	CT	myCOPD	SPACE	Rehab Guru	Active +me REMOTE
0	£4	£4	£3	£4	£2
5	£5	£4	£4	£5	£2
10	£5	£5	£4	£5	£2
15	£6	£5	£5	£6	£2
20	£7	£6	£5	£7	£2
25	£8	£7	£6	£7	£3
30	£9	£8	£7	£9	£3
35	£11	£9	£8	£11	£3
40	£14	£12	£9	£13	£4
45	£19	£16	£12	£18	£5
50	£30	£26	£17	£30	£7
55	£65	£56	£26	£64	£12
60	-£264	-£226	£64	-£258	£29
65	-£44	-£37	-£135	-£43	-£60
70	-£24	-£20	-£33	-£23	-£15
75	-£16	-£14	-£19	-£16	-£8
80	-£12	-£11	-£13	-£12	-£6
85	-£10	-£9	-£10	-£10	-£4
90	-£8	-£7	-£8	-£8	-£4
95	-£7	-£6	-£7	-£7	-£3
100	-£6	-£5	-£6	-£6	-£3

Abbreviations: CT, Clinitouch; OWSA, One-way sensitivity analysis; WD, walking distance

Less costly-less effective vs F2F PR UK COPD audit

Less costly-more effective vs F2F PR UK COPD audit

Table 12. OWSA – Impact of change in walking distance in the F2F PR arm on cost per ΔWD for the technologies

	Cost per ΔWD				
Change from baseline WD F2F, m	CT	myCOPD	SPACE	Rehab Guru	Active +me REMOTE
0	-£4	-£5	-£5	-£6	-£2
5	-£5	-£6	-£5	-£6	-£2
10	-£5	-£6	-£6	-£7	-£2
15	-£6	-£7	-£7	-£9	-£2
20	-£7	-£9	-£9	-£10	-£2
25	-£8	-£11	-£11	-£13	-£3
30	-£9	-£15	-£15	-£17	-£3
35	-£11	-£23	-£22	-£26	-£4
40	-£14	-£46	-£44	-£51	-£5
45	-£19	£407	£485	£567	-£7
50	-£31	£40	£40	£47	-£11
55	-£76	£21	£21	£24	-£27
60	£168	£14	£14	£17	£67
65	£40	£11	£11	£12	£15
70	£23	£9	£9	£10	£8
75	£16	£7	£7	£8	£6
80	£12	£6	£6	£7	£5
85	£10	£6	£5	£6	£4
90	£8	£5	£5	£6	£3
95	£7	£4	£4	£5	£3
100	£6	£4	£4	£5	£2

Abbreviations: CT, Clinitouch; OWSA, One-way sensitivity analysis; WD, walking distance

Less costly-less effective vs F2F PR UK COPD audit

Less costly-more effective vs F2F PR UK COPD audit

Table 13. OWSA – impact of uptake rates on cost savings

Uptake rates, %	Cost savings vs F2F PR (UK COPD PR audit)				
	myCOPD (first year)	Clinitouch	SPACE	Rehab Guru	Active +me REMOTE
2.5%	[redacted]	£261	£218	£255	£97
5%	[redacted]	£261	£218	£255	£97
10%	[redacted]	£261	£218	£255	£97
15%	[redacted]	£261	£218	£255	£97
20%	[redacted]	£261	£218	£255	£97
25%	[redacted]	£261	£218	£255	£97
30%	[redacted]	£261	£218	£255	£97
35%	[redacted]	£261	£218	£255	£97
40%	[redacted]	£261	£218	£255	£97
45%	[redacted]	£261	£218	£255	£97
50%	[redacted]	£261	£218	£255	£97
55%	[redacted]	£261	£218	£255	£97
60%	[redacted]	£261	£218	£255	£97
65%	[redacted]	£261	£218	£255	£97
70%	[redacted]	£261	£218	£255	£97
75%	[redacted]	£261	£218	£255	£97
80%	[redacted]	£261	£218	£255	£97
85%	[redacted]	£261	£218	£255	£97
90%	[redacted]	£261	£218	£255	£97
95%	[redacted]	£261	£218	£255	£97
100%	[redacted]	£261	£218	£255	£97

Abbreviations: F2F, face-to-face; OWSA, One-way sensitivity analysis; PR, Pulmonary rehabilitation; WD, walking distance

To explore further the uncertainty of results, while simultaneously varying the change in walking distance (effect) and the per participant cost of the digital technologies (cost), the EAG conducted a two-way analysis for Active+me that explored the impact of change in their effects on their respective costs. Results of the two-way sensitivity analysis are presented in Table 14, which aligned with that of other digital technologies.

It was unclear whether the current technology costs for Active+me REMOTE included the supervised sessions as part of hybrid PR. The EAG created a scenario analysis which assumed that the current technology costs did not include the supervised sessions. Therefore, the supervised sessions' costs were added on top of the current technology costs. This scenario reduced the cost savings for Active+me REMOTE to [redacted] from £97 (as shown earlier in Table 6) and the cost per ΔWD measures reduced by 205% compared to base case, due to the reduction in cost savings/incremental costs, as presented in Table 15.

Table 14. TWSA – Impact of ΔWD versus per participant fee on cost per ΔWD (Active +me REMOTE)

	Change from baseline WD, m	0	10	20	30	40	50	60	70	80	90	100
Per participant annual technology cost (includes license fee, staff time and training costs)	**£0**	£7	£8	£10	£13	£18	£32	£127	-£65	-£26	-£16	-£12
	£50	£6	£7	£9	£11	£16	£29	£113	-£58	-£23	-£14	-£10
	£100	£5	£6	£8	£10	£14	£25	£98	-£50	-£20	-£12	-£9
	£150	£4	£5	£6	£8	£12	£21	£83	-£43	-£17	-£11	-£8
	£200	£4	£4	£5	£7	£10	£17	£68	-£35	-£14	-£9	-£6
	£250	£3	£3	£4	£5	£8	£14	£54	-£27	-£11	-£7	-£5
	£300	£2	£2	£3	£4	£6	£10	£39	-£20	-£8	-£5	-£4
	£350	£1	£2	£2	£2	£3	£6	£24	-£12	-£5	-£3	-£2
	£400	£0	£1	£1	£1	£1	£2	£9	-£5	-£2	-£1	-£1
	£450	-£0	-£0	-£0	-£1	-£1	-£1	-£5	£3	£1	£1	£1
	£500	-£1	-£1	-£2	-£2	-£3	-£5	-£20	£10	£4	£3	£2

Abbreviations: TWSA, Two-way sensitivity analysis; WD, walking distance

Less costly-less effective vs F2F PR UK COPD audit

Less costly-more effective vs F2F PR UK COPD audit

More costly-less effective vs F2F PR UK COPD audit

More costly-More effective vs F2F PR UK COPD audit

Table 15. Scenario analysis

	Incremental effect (ΔWD, m)	Incremental effect (ΔWD, MCID units)	Incremental effect (%ΔWD)	Incremental costs, £	Cost per ΔWD, m	Cost per ΔWD, MCID units	Cost per %ΔWD	Change from base case value, %		
								Cost per ΔWD, m	Cost per ΔWD, MCID units	Cost per %ΔWD
Alternative effectiveness data source for SPACE for COPD										
SPACE for COPD (ISWD data source Bourne et al 2022)	-39.18	-0.825	-25%	Same as base case	£6	£265	£889	-59%	-113%	-113%
Alternative 6MWT MCID cut-off										
Clinitouch	Same as base case	-0.004	Same as base case			£70,649	Same as base case	-	-80%	-
myCOPD		-0.470				£476				
Rehab Guru		-0.467				£546				
myCOPD annual per participant total cost based on 5% uptake (first year cost)										
myCOPD	Same as base case			[redacted]	[redacted]	[redacted]	[redacted]	-40%		
myCOPD annual per participant total cost based on 'legacy' contract per participant fee										
myCOPD	Same as base case			[redacted]	[redacted]	[redacted]	[redacted]	16%		
Clinitouch per participant costs derived based on per clinician per year										
Clinitouch	Same as base case			[redacted]	[redacted]	[redacted]	[redacted]	-5%		
Active+me REMOTE annual per participant total cost including supervised sessions for hybrid PR										
Active+me REMOTE	Same as base case			[redacted]	£7	£345	£476	-205%		

3.4. Discussion and implications

The EAG presents here results from one [redacted]. No eligible evidence for Active+me REMOTE was available for the original EAG report. The new Harefield Hospital Study provided data [redacted] Results for some outcomes [redacted] However, it was not clear whether the change scores presented were against baseline or [redacted], which adds uncertainty to the interpretation (the EAG assumed change scores were vs baseline for the economic evaluation).

In the evidence gap analysis in the original EAG report, all categories were red, as no evidence was identified. Based on the Harefield Hospital Study, most categories could move to amber. However, only one relevant study is available, and no categories would move to green, reflecting how there is still considerable remaining uncertainty.

In conclusion, one [redacted] was provided for ACTIVE+me REMOTE. This is the first relevant evidence for this technology for this appraisal. This evidence generally moves the picture from ‘no evidence’ to ‘uncertain evidence’. However, considerable uncertainty remains regarding the potential benefits of ACTIVE+me REMOTE in this population. The updated CCA using the ISWD data from Harefield study indicated that Active+me REMOTE could be cost saving, though slightly less effective compared to face-to-face PR as per 2015 audit data. The exploratory CEA also indicated that when the UK COPD pulmonary rehabilitation audit data was used for face-to-face pulmonary rehabilitation, Active+me was found to be cost saving and less effective similar to other digital technologies.

4. REFERENCES

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