IMI1 Final Project Report Public Summary

Project Acronym: PROactive

Project Title: Physical Activity as a Crucial Patient Reported Outcome in COPD

Grant Agreement: 115011
Project Duration: 01/09/2009 – 31/05/2016

Executive summary

The executive summary will be made publically available, and therefore should not include information deemed as confidential by the consortium. It should be concise (preferably no more than 40 pages), comprehensive and should capture the updates for the last reporting period as well as the overall outputs of the project and its impact. It shall at least cover the following items:

1. Project rationale and overall objectives of the project

Physical activity (PA) is recognized as an important aspect of how patients with COPD perceive the burden of their disease. The link between physical activity and the extra-pulmonary consequences of COPD is becoming increasingly clear. The PROactive consortium has now developed a method to assess physical activity objectively using validated activity monitors, used together with a set of questions which combine to capture the experience with PA from a patient perspective. If the two hybrid tools (a daily diary and a clinic visit tool) prove to be valid in other COPD populations, languages and cultures, PROactive will have met its overarching goal: 'develop and validate a new Patient Reported Outcome (PRO) capturing the patients' experience with PA'. Our project has followed the regulatory guidelines on the development of PRO tools, published by the United States FDA and the European EMA.

2. Overall deliverables of the project

The main scientific deliverables in the project are to *1) develop a thorough and systematic set of literature reviews to inform the project; 2) select activity monitors capable of capturing the amount of PA with a degree of precision that allows them to be used in the validation of the new PRO tool and in conjunction with the new PRO in clinical research; 3) do extensive qualitative research on how patients experience PA, with the aim to a) develop a conceptual framework around PA and b) select the most appropriate items (questions) for the PRO, based on patient input; 4) to conduct a study to reduce the number of items to provide an efficient and initially validated version of the PRO and confirm the conceptual framework; 5) to complete the validation process and deliver final validated PRO tools in at least 10 languages of the EU.*

The deliverables in Italic have now been met. Deliverables up to 4) have been published in the peer reviewed literature. Manuscripts for several of the studies for deliverable 5) are being developed and their results have been summarized in the documents submitted to the European Medicines agency. Outside of these deliverables related to the scientific work, there is a set of deliverables related to the project management, training, ethics and dissemination of the project (towards patients, scientists and regulators).

PROactive clinical visit PRO.

Amount (To be combined with information from activity monitors)		
walk_c	In the past 7 days, how much walking did you do outside?	**0**: None at all **1**: A little bit (about 10 minutes every day) **2**: Some (about 30 minutes every day) **3**: A lot (about 1 hour every day) **3**: A great deal (more than 1 hour every day)
outside_c	In the past 7 days, how many chores did you do outside the house? Some examples are gardening, taking the rubbish out, or doing small errands	**0**: None at all **1**: A few **2**: Some **3**: A lot **4**: A large amount
Difficulty		
dressed_c	In the past 7 days, how much difficulty did you have getting dressed?	**4**: None at all **3**: A little bit **2**: Some **1**: A lot **0**: A great deal
outabout_c	In the past 7 days, how much difficulty did you have getting out and about?	**4**: None at all **3**: A little bit **2**: Some **1**: A lot **0**: A great deal
avoid_c	In the past 7 days, how often did you avoid doing activities because of your lung problems?	**4**: None at all **3**: Rarely **2**: Sometimes **1**: Frequently **0**: All the time
general_c	In the past 7 days, how breathless were you in general during your activities?	**4**: None at all **3**: A little bit **2**: Moderately **1**: Very **0**: Extremely
strength2_c	In the past 7 days, how often did you lack physical strength to do things because of your lung problems?	**4**: None at all **3**: Rarely **2**: Sometimes **1**: Frequently **0**: All the time
tired_c	In the past 7 days, how tired were you in general during your activities?	**4**: None at all **3**: A little bit **2**: Moderately **1**: Very **0**: Extremely
break_c	In the past 7 days, how often did you have to take breaks during your physical activities?	**4**: None at all **3**: Rarely **2**: Sometimes **1**: Frequently **0**: All the time
breathless1_c	In the past 7 days, how breathless were you when walking on level ground indoors and outdoors?	**4**: None at all **3**: A little bit **2**: Moderately **1**: Very **0**: Extremely

recovertm_c	In the past 7 days, how much time did you need to recover from your physical activities?	**4**: None at all **3**: A little bit **2**: Some **1**: A lot **0**: A great deal
consideration_c	In the past 7 days, did you need to consider your lung problems when you planned your activities? Examples are a trip out, an appointment or expecting visitors	**4**: None at all **3**: A little bit **2**: Sometimes **1**: A lot **0**: A great deal

Calculation of the score is done as indicated in the manual of procedures available from the consortium and published in the European Respiratory Journal (Gimenez, Eur Respir J 2014)

3. Summary of progress versus plan since last period

The project ended on the planned date as per last amendment. Although this is 18months later than initially foreseen, the project stayed within projected budget lines and delays have been properly justified in previous reports and formal amendments granted. By the end of the project in May 2016 the intended work was delivered. Unfortunately the interaction with the European regulators could not be scheduled before the end of the project (despite timely submission by the consortium in October 2015). The date for the meeting was postponed to early June2016, when the face to face meeting in London took place. All work in the last reporting period progressed as scheduled according to the updated description of work. The only modification made was that the task of the last report on 'ethics' was replaced by a 'final feedback moment' with the patient stakeholder in the project. This was conducted adopting a novel approach using a webinar (see below) and was carried out by the same partner (Dutch Lung Foundation) No budget changes were required.

In summary all deliverables and milestones were in place by the end of the project, however we are still awaiting the draft qualification opinion from the EMA.

4. Significant achievements since last report

Since the last reporting period the main focus of the PROactive project has been the completion of the PROactive studies in Work package 6. In the last reporting period the recruitment of a number of WP6 studies had started. At the end of the project these studies have collectively provided the required patient numbers to answer all questions posed in the validation statistical analysis plan**.** This plan summarized the study designs of the different studies included in the further validation work package (PHYSACTO, T9, EXOS, Mr PaPP, Urban Training). It also outlined how the PROactive scores were calculated and included a section on the data management, including how data from the different sources were to be merged. Lastly it contained an a prori plan on validity criteria and analysis of responsiveness for the two PROactive tools (C-PPAC and D-PPAC). The statistical analysis plan was locked in May 2015, prior to the analyses of WP6 studies. In this work package (WP6) the PROactive tools were used by the academic consortium partners (*Mr PAPP study and Rehabilitation study*) and by some EFPIA members in clinical studies (*ExOS to some extent and PHYSACTO*). Altogether 1330 patients were recruited, 81% of which could be used in the PROactive analyses (1083 patients; 723 of which were used for analyses of the daily PRO, 636 patients for the clinical visit version). Taken together these trials have generated sufficient data to gain information on the use and usability of the PROactive tools in clinical research. One additional study, initiated by Almirall and subsequently 'executed' by AZ will provide more information outside the project window. Data will be available in mid-October 2016. Collectively the results of the different studies provided further information on the validity, as well as information on responsiveness and the minimal important difference (important to allow responder analyses). After fruitful discussion with the European regulators at EMA the final method of scoring for the PROactive tools contains a total score (mean of the two domains) and two domain scores capturing 'amount' and 'difficulty' as the essential components of the PROactive score. Publication of the Mr PAPP study is currently under revision for a major respiratory journal and the PHYSACTO study has been presented at the European Respiratory Society conference in two poster presentations. These studies formed the basis to analyse the responsiveness of the D-PPAC and C-PPAC. Importantly, the studies are anticipated to

have different effects on physical activity experience, although so far no valid interventions to enhance the relevant domains of PA are available. In the Mr PAPP study patients are offered a telecoaching program to help achieving a higher step count. As this program is geared to 'activate' patients without improving physical fitness or health status, we anticipate to see effects particularly on the domain 'amount' of the PROactive scale, without important changes in the domain of difficulty. The 'total score' for physical activity experience is expected to improve. In the PHYSACTO study patients are all receiving a telecoaching intervention. On top of this intervention patients are receiving placebo pharmacotherapy, a single or dual bronchodilator or a dual bronchodilator+an exercise training intervention. Here we anticipate that the domain of difficulty might improve as soon as a bronchodilator is associated to the treatment.

Mr PaPP indeed showed a significant improvement in physical activity levels without changes in exercise tolerance or symptoms. Physacto showed an improvement in physical activity levels in all patient groups with significant improvements in exercise tolerance and symptoms when bronchodilators and also exercise training were added. The studies conducted therefore may indeed offer a good platform to evaluate the responsiveness of the PROactive scores.

During this European Respiratory Society conference the general results of WP6 in terms of responsiveness were also presented based on the Mr PAPP study results. The data show that –as expected with this design- the amount domain improved, without changes in difficulty in the group that received telecoaching. However in patients that reported less difficulty during daily life on a global rating scale, indeed less difficulty on the PROactive score was detected. We concluded that the PROactive scores are valid measures of these two essential domains of patient experience with PA.

	Total score (0-100)			Amount score (0-100)			Difficulty score (0-100)		
	Baseline	Final	SRMs	Baseline	Final	SRMs	Baseline	Final	SRMs
	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)	m (SD)
Study arm									
Usual care	70 (13)	67 (15)	-0.3 (1.0)	65 (17)	62 (18)	-0.3 (0.9)	75 (14)	73 (16)	-0.2 (1.1)
Telecoaching intervention	69 (11)	71 (14)	0.2 (1)	63 (15)	66 (18)	0.2 (1)	75 (13)	75 (14)	0.01 (0.9)
Self-reported change in amount									
Less active	65 (13)	61 (14)	**-0.6 (0.9)**	61 (17)	55 (18)	**-0.5 (0.8)**	69 (15)	68 (17)	-0.3 (1.2)
No change	71 (12)	71 (13)	-0.1 (0.9)	65 (16)	65 (17)	0.02 (0.9)	77 (13)	76 (14)	-0.2 (0.9)
More active	71 (10)	75 (11)	**0.5 (1.0)**	65 (14)	70 (16)	0.4 (1.1)	78 (12)	80 (13)	0.2 (0.8)
Self-reported change in difficulty									
More difficult	64 (12)	59 (14)	**-0.7 (0.9)**	61 (17)	55 (18)	**-0.5 (0.9)**	67 (13)	63 (15)	**-0.6 (1.1)**
No change	71 (12)	71 (13)	0.02 (0.9)	65 (16)	65 (17)	0.04 (0.9)	77 (13)	77 (13)	-0.0 (0.9)
More easy	72 (10)	76 (11)	**0.5 (1.0)**	65 (14)	70 (18)	0.4 (1.1)	79 (12)	81 (12)	0.3 (0.8)

Table 1 C-PPAC scores responsiveness as presented by Garcia-Aymerich et al at the Eur Respir Soc Conference Sept 2016

The use of PROactive tools by third parties was further facilitated by streamlining the process of permitting use via a memorandum of understanding between the consortium and third party and by working out a very detailed user manual.

Several scientific studies of WP6 have provided –besides information on the PROactive tools- unique insight in the effectiveness of innovative interventions or combinations thereof. In the academic Mr PaPP study convincing evidence was presented that a telecoaching program using a telephone based application and feedback on physical activity was successful in enhancing physical activity levels of patients with COPD. The intervention increased step counts significantly and to a clinically relevant extent and was shown to be particularly effective patients with better preserved exercise tolerance.

The telecoaching intervention *per se* had no clinically important effect on exercise tolerance or health related quality of life. These findings from this multicentre study support data obtained previously in a single center study (Mendoza Eur Respir J 2014). The telecoaching program designed specifically for this study has been 'recycled' in the EFPIA driven 'Activate' study (AZ, which will deliver results in Oct 2016). The PHYSACTO study (BI) used also a behavioral coaching program somewhat inspired by Mr PaPP. In the PHYSACTO trial, this behavioral self management program was, however more specifically designed towards face to face contacts (Bourbeau BMJ open 2016). The PHYSACTO study was a trial with four arms spanning contemporary management of patients with moderate COPD, including physical activity coaching and self-management, adding a single long acting bronchodilators (Tiotropium), adding a second bronchodilator (Tiotropium and Olodaterol) and adding an exercise training program. The study delivered results in January which are now being prepared for publication. This trial is an example of how several non-pharmacological treatment options are blended with pharmacotherapy. The trial showed that with increasing bronchodilation and the combination with exercise training, exercise endurance increased gradually. Physical activity was enhanced by the behavior change program, but adding further bronchodilator therapy and exercise training did not further enhance physical activity.

Last but not least, the results of the PROactive project were presented again to patients (in the initial phases of the project patient input was key to the development of the project and the PROactive tools). Several comments were obtained from patients on the telecoaching application, which can serve to further improve this intervention beyond the project. The application consist of a mobile phone app that provides the patients with an interface to be semi-automatically coached (physical activity goals, feedback, encouragement, interactive goal setting and adaptation) as well as an investigator backend that allows the patient management through the coaching period. Meanwhile, a further improved version 2.0 of the application has been developed by KUL in the context of a locally supported project. In presenting the results of the PROactive project to patients, it was particularly reassuring that they related very strongly to the concept of physical activity and to both PROactive tools developed. This input from patients was gathered through a webinar which was centrally managed (Logistics through the European Respiratory Society and the Dutch Lung Foundation) and locally facilitated by moderators in all clinical sites involved in the projects. This setup guaranteed an efficient running of the webinar with translations provided by regional investigators at no cost. Feedback from patients afterwards revealed that translation during such events is essential to guarantee success in the 'inclusive' running of such forms of patient input.

5. Scientific and technical results/foregrounds of the project

The main deliverables that were anticipated in the program were the Patient Reported Outcome Tools to capture experience of physical activity for patients with COPD. These have been delivered and submitted to the European Medicines Agency for their evaluation under the procedures for the qualification of novel drug development tools. The PROactive instruments exists in two versions, a daily diary and a weekly recall questionnaire for use in the clinic. Two activity monitors have been calibrated to be used in these hybrid tools (either monitor can be used with each questionnaire).

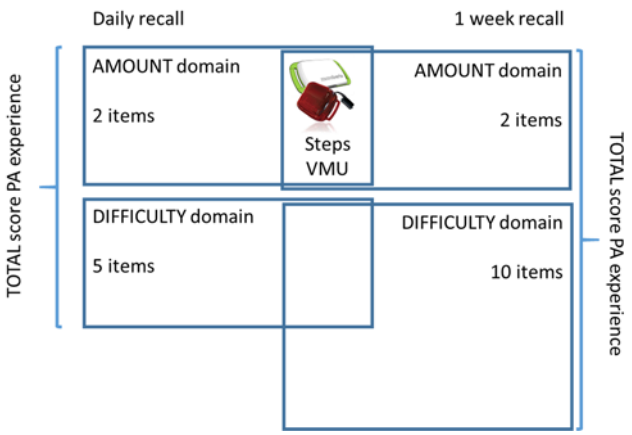

Fig 1 schematic representation of both PROactive PRO tools. Daily and weekly recall versions available with two activity monitors.

Databases of well phenotyped COPD patients were obtained through the larger clinical trials of work Package 4 and work package 6. For all development and psychometric testing, standard operating procedures were worked out by the consortium and applied in the study protocols and training workshops ensured proper training of study staff

A novel intervention using tele-coaching to enhance physical activity in patients with COPD has been developed and applied successfully in a multicenter study. The tele-coaching program was slightly modified and adopted in the EFPIA study conducted by AZ (finalized). This shows that the results from the PROactive project can indeed be incorporated in future projects. Importantly the tele-coaching program was implemented in an SME's platform (Linkcare, Spain), which was used both in MrPaPP and in 'ACTIVATE'.

A prototype of a 'complex design' study including several contemporary elements of proper COPD management has been described by BI (the Physacto study protocol published in two BMJ-open protocol design papers Troosters et al BMJopen 2016 and Bourbeau et al BMJopen 2016).

A novel way to obtain direct patient involvement was used by a 'webinar' where the main results of the PROactive developments and comments by patients on the telecoaching application and on the PROactive tools were gathered from six EU locations using local moderators helping to trnslate. This allowed to get input from genuine patients suffering from COPD, rather than from 'professional patients' selected on a basis of speaking English, which undoubtedly results in a biased patient group. The patient groups in the different locations were enthusiastic about the PROactive developments and recognized their problems as being captured with the PROactive tools. In general we also found support for the conceptual model previously outlined by Dobbels et al Eur Respir J 2014.

6. Potential impact and main dissemination activities and exploitation of results

Please explain how the project scientific/technical outputs contribute to the overall IMI objectives:

- *to provide socio-economic benefits for European citizens,*
- *to contribute to the health of European citizens,*
- *to increase the competitiveness of Europe and help to establish Europe as the most attractive place for biopharmaceutical research and development.*

Please outline how the project outputs have/will have the potential to be rapidly and broadly spread and taken up within the scientific/industrial community and healthcare professionals.

The PROactive project has provided knowledge on physical activity in a population of patients where long term physical inactivity sits in the core of the development of burden of the chronic disease. In addition, physical activity is also an important target for therapy and is amenable to change. Such changes are considered by patients as very meaningful to their lives with COPD. During the project and partly due to the PROactive consortium the impact of physical inactivity in COPD has become clearer and tackling physical inactivity has been recognized as a key target for COPD management. The PROactive project renders results that are directly applicable for COPD patients (some 10% of the European population over 50 years old) as well as for researchers in academia and industry conducting studies that aim at improving COPD management with pharmacotherapy or non-pharmacotherapeutic interventions.
Throughout the project the PROactive consortium has met with representatives of EMA with the intent to qualify the PROactive tools as novel drug development tools which will facilitate the use of the tools in drug development programmes and subsequently the inclusion of information on physical activity measured by the PROactive tools within SmPC information for prescribers.

1) Assessing physical activity
    a. From a wide range of activity monitors, three were classified as valid to assess physical activity across the spectrum of the disease and two of these were moved forward in the PROactive studies in WP4 and 6: the Dynaport Activity Monitor (McRoberts, The Haegue, NL) and the GT3X (Actigraph, Pensacola, US)
    b. A concept describing physical activity experience in COPD was identified which ultimately resulted in two complementary domains, recognized by patients: 'Amount of experienced activity' and 'Difficulty experienced with physical activity'
    c. Two patient reported outcome tools were developed and validated and are now ready for use in clinical trials by academic and industry researchers. The fact that that agreements outside the consortium were made with third party pharmaceutical industries as well as several third party academic consortia provides proof of direct interest by researchers.
2) Addressing physical activity in COPD
    a. The consortium provided direct evidence on the importance of physical activity and its determinants as well as consequences to help guiding interventional studies
    b. The consortium also provided evidence on the efficacy of several contemporary interventions aimed at enhancing physical activity. The efficacy (or lack thereof) of these interventions was shown for objectively assessed PA as well as patient experience with Physical activity. Tele-coaching, rehabilitation and bronchodilator therapy are clearly shown to have complementary effects on physical activity and therefore are beneficial to enhance patient's health.
3) This project resulted in several PhDs and boosted the career of several biomedical researchers. Nine PhDs were the direct spin off of the project (Hans Van Remoortel, Elena Gimeno Santos, Heleen Demeyer, Miek Hornikx, Yogini Raste, Zafeiris Louvaris, Eleni Kortianou, Maroula Vasilopoulou, Ivan Duenas-Espin). For several postdoctoral researchers it was a step up to a successful academic career through the PROactive network. Two of them

(Dr Heleen Demeyer and Dr Zafeiris Louvaris) received a long term fellowship of partner ERS to conduct research at another PROactive partner institute (Heleen Demeyer, mobililty to CREAL; Zafeiris Louvaris, mobility to KU Leuven)

7. Lessons learned and further opportunities for research

Please indicate how the collaboration in a public private partnership (PPP) has been an added value to achieve the objectives of the project.

From your experience, please propose any recommendations/ solutions which could be useful for a PPP.

In view of your project achievements, please provide your views on potential new research to further advance the field.

1) Public Private Partnership added value

The collaboration of academic researchers, EFPIA researchers, SME input and patients has clearly been essential in forming the foundation of the developed Patient Reported Outcome tools to capture physical activity and their translation into several EU languages. Translations of the interviews from three source languages of the patients into English, provided/facilitated and managed by the SME were essential to allow development of a tool with different source languages. This in itself is rather unique as typically PROs are developed in one source language and translations are subsequently made and validated. Translations of the PROactive tool into the languages used in the clinical trials of WP6 were subcontracted by the industry partners, who are used to translating PROs for clinical trial purposes. The know-how of several partners has been essential to translate the FDA 'guidance to industry' for the development of PROs into a concrete road map with specific statistical plans in the development and validation of the PROs. This road map can clearly help future PRO developers.

2) Recommendations for a PPP

The PROactive project was among the first call projects. The new funding scheme has subsequently undergone changes. In our experience there are important differences in the *modus operandi* of public and private partners. Differences exist in the way funding is handled, commitments are taken and the stability within a research environment.

a) Funding is essential to support the research activities of academic partners, whereas EFPIA members contribute 'in kind' and this makes these partners less dependent of the additional funding and project results. Possible solutions have been proposed by the consortium in the close out meeting with IMI-JU. In the opinion of the project management team all possible efforts should be taken to ensure long-term commitments of partners (particularly those with in-kind contributions) for the duration of the project. The IMI-JU funding scheme should perhaps also foresee or unavoidable losses of commitment for strategic reasons.
b) Commitments taken by public partners are typically covered by funds in a particular WP and can be guaranteed over a long project period. For private

partners commitments depend very much on key members of staff which has proved to be volatile over the course of the project. Several key figures in our consortium have moved companies. Sometimes their presence continued as member of another partner, sometimes the expertise (and concomitant commitment) was lost. This can cause problems if the expertise lost is vital to a project. Over the course of the project for examples several EFPIA members decided to reduce the staff in 'PRO-units' which could have caused problems. Clearly this has affected the priority given to a project developing a PRO by these partners.

c) Stability of the research environment: Where an academic centre thrives on research, a private partner also depends on strategic decision of the company and its stakeholders. The PROactive project effectively lost one EFPIA member (Pfizer) after the company decision to drop its respiratory portfolio during the course of the project. Another partner remained on board, but also sold its respiratory portfolio (lucky for the project to another PROactive partner).. Such decisions have important consequences in terms of financial contributions. If this would happen with a public partner the partner could easily be replaced and funding reallocated to the new partner. Since EFPIA partners depend less of funds this is more difficult to do with private partners. As suggested above the IMI-JU organization should consider having a structured approach to such events where the partner that leaves ensures continuity either by attracting new in-kind resources or through a cash contribution allowing the project to take over essential tasks.

d) In this first round of IMI-JU funded projects the initial efforts needed to take place in Europe. While we understand that the bulk of the development needs to be conducted in Europe, more options should be made available to also use resources from US or elsewhere. In the case of the present project, the limited initial input from the US has made it very difficult to file a case for the PROtools developed with the US regulators (FDA).

4) Possible future research

The consortium has expressed an interest in 1) safe-guarding the PROactive developments and 2) continued development of the tools in an unfunded follow-on consortium. A business plan and memorandum of understanding has been agreed by partners and a renewed consortium agreement is being constructed. Within the newly established ERS Research Agency there is the potential to host the data of the COPD cohorts established in the several completed studies. If new funds can be attracted these patients can be followed up and information on the importance of PA in driving disease progression can be obtained. This would require new funds. The continuation of the consortium is considered a first step in acquiring such funds.

It is realistic to have the ambition to further develop the PRO tools for use in other respiratory diseases or even outside of the respiratory area.