INTRODUCTION
Detailed guidance for the use of patient-reported outcomes (PROs) as endpoints in clinical trials where a label claim has been desired for approval by FDA (2009). However, no such direct guidance currently exists for chronic obstructive pulmonary disease (COPD) patients. ClinROs are endpoints used to assess the impact of therapies on PROs. ClinROs are primary endpoints, comprised of PROs to PLOS in approximately 3.1 (Burke, 2010). Although regulatory guidance for the use of ClinROs as clinical endpoints in supporting label claims has not yet been produced, it has been indicated that the standards applied in the PRO guidance will apply to all clinical outcomes including ClinROs (Burke 2011, Nixon 2012).
ClinROs have been defined as an endpoint where “an assessment is determined by an observer with some recognized symptoms.” Such endpoints may be captured following patient clinical interview, conduct of specific tests, or from review of medical files. Nixon and Galeps (2010) have previously reported the level of evidence required for PRO standards to applied to four widely used ClinROs. They found several problems and concluded that ClinROs have been relatively underrepresented for regulatory purposes.

OBJECTIVES
The aim of this study was to present a pathway for effective ClinRO dossier development with the objectives being to:
1. Assess the extent of use of ClinROs in drug development and label claims
2. Identify examples of widely used ClinROs, and evaluate these from the standard set in the literature
3. Provide a step-by-step account of the various stages in effective ClinRO dossier development

METHODS
Key terms were searched in published literature and clinical trial information. In December 2012: "clinics reported outcomes", "ClinRO measurement", and "ClinROs”. In PubMed, the search was limited to the key terms appearing in "The abstract" in ClinicalTrials.gov on advanced search was used with the same key terms entered as “Outcome measure” in the clinico-terminology database. The number of hits were recorded.
ClinROs were selected for assessment from the literature. The search from the literature yielded the most hits of the four key terms: 11462 in PubMed and 5113 in ClinicalTrials.

RESULTS
The key term ‘clinical assessment’ yielded the most hits of the four key terms: 11632 in PubMed and 3173 in ClinicalTrials.gov. There was a greater number of ClinROs from PubMed and ClinicalTrials.gov results were used. The name of the ClinRO as an ‘outcome measure’ in ClinicalTrials.gov with number of studies documented.

The development approach and evidence for the content validity of each of these measures were assessed by obtaining the name of the ClinRO as an ‘outcome measure’. We identified three widely used ClinROs and evaluated them in line with the FDA PRO guidance. The three ClinROs evaluated were:
• Six Minute Walk Test (6MWT)
• Global Impression of Improvement (CGI)
• Mayo Clinic Scleroderma Disease Activity Index (MCSI)

Six Minute Walk Test (6MWT):
Originally developed for COPD patients with pulmonary disease (Bell 1982) and has since been used to assess cardiorespiratory function. The 6MWT measures the distance the patient can walk in six minutes. Guidance by the American Thoracic Society (2002) recommends that it be conducted indoors, at a flat, straight, enclosed corridor with a hard surface, unless the weather is comfortable enough to be performed outdoors. A 30-meter length course is recommended, with turnaround points at each end marked with a cone. As an outcome measure in ClinicalTrials.gov it was listed to a large extent, with several studies documented.

Global Impression of Improvement (CGI):
The CGI was developed for use in hospital inpatient trials for patients with psychiatric disorders, particularly psychiatric illness (Guy 1976). The CGI was not applicable of a scale for use in trials on any clinical condition. It was 1=very ill to 7=not at all ill. Global Impression of Improvement scales scored 1=very ill to 7=very much better. Efficacy index is a change in CGI, indicating improvement, with 1=very much worse to 7=very much improved to 7=very much worse. Efficacy index is a acceptable, evidences a change of 0.6 or greater.

Mayo Clinic Scleroderma Disease Activity Index (MCSI):
The MCSI is a 5-item, 11-point composite disease activity index that yields a score of 0-11. It takes 1-2 minutes to complete (Guy 2000). The MCSI was listed as an outcome measure in 825 studies (DOCTRINE, 2009).

CONCLUSIONS
This review of these three ClinRO adds to a growing body of work that identifies gaps in their original development and subsequent measurement properties. We compared the PROs used for ClinROs with the current standards established by the FDA. The ClinROs reviewed here developed these clinical outcomes in 1997; 73(3):159-71. Sandborn WJ, Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study. New England Journal of Medicine. 1997;337(14):929-35.

Our review of the evidence for these three widely used ClinROs, identified that, on the basis of their original development free they fall short of the measurement requirements necessary by the FDA. We also identified that subsequently reported measurement properties for these ClinROs is very many, but not all, of the gaps observed in their original development and these findings, the corner label of guidance for ClinRO use in drug development and label claim we propose the following pathway to effective ClinRO dossier development.

Fig 1 Pathway

Pathway for Effective ClinRO Dossier Development
Our review of the evidence for these three widely used ClinROs identified, on the basis of their original development free they fall short of the measurement requirements necessary by the FDA. We also identified that subsequently reported measurement properties for these ClinROs is very many, but not all, of the gaps observed in their original development. We identified these and the corner label of guidance for ClinRO use in drug development and label claim we propose the following pathway to effective ClinRO dossier development.

REFERENCES


Concurrent validity was assessed using the correlation of the measure with other indicators of change, such as responsiveness. In ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observations in ophthalmology, the PROs are generally assessed using the relationship of the PROs to the clinician’s observations. The relation of the PROs to the clinician’s observ...