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Protocol for a prospective multicentre cohort study to develop and validate two new outcome measures for patients with inflammatory bowel disease.

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Abstract:

Introduction: Most of the health related quality of life (HRQoL) measures for patients with inflammatory bowel disease (IBD) were designed to be used in outpatient settings and are, therefore, not suitable for use in acute inpatient settings. None of the currently used clinical severity indices for patients with IBD have been properly validated. The aim of this study is to describe the development of a new health related quality of life questionnaire and a clinical severity index for patients with ulcerative colitis or Crohn's disease that are short , valid and suitable at any stage of their disease. These new outcome measurement tools will be easily used at the point of care, and invaluable monitoring tools for clinical care, audit and research.

Methods and analysis: This is a prospective multi-site validation study of two new outcome measures, the Crohn's and Colitis quality of life (CCQ) questionnaire and the Clinical IBD severity score (CISS). We plan to recruit patients with ulcerative colitis or Crohn's disease. Questionnaire items will be selected through extensive literature review and a focus group involving patients, methodologists, statisticians and IBD specialists. The CCQ questionnaire will be completed by patients attending IBD clinics, having endoscopy procedures or when admitted to hospital. The CISS will be completed by clinicians while assessing patients with IBD. Psychometric analysis will be carried out to test the validity and the reliability of the questionnaires and determine the potential to produce shorter versions of CISS and CCQ. The construct validity of the CCQ will be tested against short form-12 (SF12) and the European Quality of Life Five Dimensions (EQ5D). The construct validity of CISS will be tested against biochemical markers, clinical and endoscopic indices to assess severity.

Ethics: This study was approved by the South East Wales Research Ethics Committee (Ref 11/WA/0239).

Article summary:

Article focus:

- None of the currently used clinical severity indices for patients with inflammatory bowel disease (IBD) have been properly validated.
- Most of the health related quality of life (HRQoL) measures for patients with IBD have been designed for use in outpatient settings and are, therefore, not suitable for use in acute inpatient settings
- This article describes the protocol for a prospective multi-site validation study of two new outcome measures; the Crohn's and Colitis Health related quality of life (CCQ) questionnaire and the Clinical IBD severity score (CISS).

Key measures:

- The main focus of the article is the development and validation of two outcome measures to assess the quality of life and disease severity of patients with IBD.
- This article provides an insight into the methods used to develop and validate new outcome measures which can applied to any disease.

Strength and limitations of this study:

- The CISS will be the first fully validated clinical severity index for patients with IBD.
- The CCQ will be the first health related quality of life tool that will be applicable to all types and presentations of IBD.
- It may be difficult to recruit adequate numbers of patients with less common presentations of IBD like perianal Crohn's disease or patients with extra-intestinal manifestations.

Introduction:

Inflammatory bowel disease (IBD) affects approximately one person in every 250 in the United Kingdom population[1]. The cost of IBD to the NHS has been estimated at about £720 million per annum, based on the prevalence and an average cost of £3,000 per year per patient [2]. The lifetime medical costs associated with the care of IBD are comparable with major chronic diseases such as diabetes mellitus or cancer [2]. Anti Tumour Necrosis factor α (Anti TNF-α) drugs are new and effective biological treatments for both ulcerative colitis [3] and Crohn's disease [4] but long-term outcomes are still unknown and there are a number of safety issues [5]. Therefore, the National Institute for Health and Clinical Excellence (NICE) has recommended the establishment of a Registry for patients with IBD treated with biological therapy [6]. Assessment of response to treatment will require measurement of both HRQoL and disease severity.

HRQoL questionnaires are often employed as measures of health status and are important outcome measures in clinical trials. They should form an integral part of any outcome monitoring efforts but are often omitted from large scale registries because of constraints on the amount of data these registries can collect. To facilitate adoption of HRQoL measures in large IBD registries, it is important to develop instruments which are short and easy to complete, yet valid, reliable and applicable to all IBD patients.

IBD has a great impact on the quality of life as it is not curable and follows an unpredictable relapsing and remitting course with significant variation in the pattern and complexity of symptoms that may affect each patient, sometimes leading to hospital admission, surgery and bowel resection, which may leave the patient with a stoma. There are several specific HRQoL measurement tools for patients with inflammatory bowel disease[7, 8, and 9]. However, all of them have been designed for use in the outpatient setting with stable patients and there is no HRQoL instrument that is validated for use both in the community and by patients who are acutely ill, have a stoma or perianal disease.

In clinical practice, assessing disease severity is an important part of IBD management and a standardized and quantitative evaluation of the severity of IBD is needed for the registry. Due to the varied presentations of IBD, a number of clinical indices have been put forward using different parameters which are based on different principles [10, 11]. In order to be widely utilised and generalisable, the index should include as few items as possible which are easily obtainable in any clinical setting and applicable to the majority of patients. An index should also possess the required psychometric properties such as validity and reliability [15]. In IBD,

there are several different disease severity indices available[10, 11]. However, none of them have been properly validated. Therefore, for a successful IBD registry, there is a need for a short yet reliable and valid severity score index to assess response to treatment and to detect early relapse for all types and presentations of IBD.

Aim:

The aim of the study is to develop valid and reliable HRQoL and a disease severity measurement tools that are suitable for use with patients at any stage of their IBD. These tools will be easily recorded at the point of care to support their use for a registry of patients with IBD.

Objectives of the study:

1. To validate a HRQoL questionnaire (Crohn's and Colitis Quality of Life (CCQ) questionnaire) and derive a short form (Short CCQ) that is suitable for acute and stable patients with IBD and covers patients with a stoma or fistula.
2. To validate a single clinical severity index (Clinical IBD severity index (CISS)) and derive a short form that is suitable for all types and presentations of IBD.

Methods and analysis:

Developing the outcome measures:

1. The Crohn's and Colitis Health related quality of life questionnaire

The initial version of the Crohn's and Colitis Health related quality of life questionnaire (CCQ) will be based on the UK Inflammatory Bowel Disease Questionnaire (UK IBDQ) [9] that was developed and validated in 2000. An extensive literature review will be carried out to identify supplementary items to reflect the wide range and frequency of symptoms of IBD when patients are seen as outpatients, inpatients, with perianal disease and with a stoma. The first draft of CCQ will be an inclusive as possible to cover all patients with IBD. We will validate the CCQ with a wider group of patients to include patients with both Crohn's disease (CD) and Ulcerative colitis (UC) as well as patients with a stoma and Crohn's perianal disease. The questionnaire will be examined by IBD specialists, methodologists and statisticians to ensure good face and content validity of the items. To ensure that the resulting

questionnaire is clear to patients, we will conduct a feasibility study, asking a small sample of patients to complete the questionnaires.

2. The Clinical IBD Severity Score (CISS)

The development of Clinical IBD Severity Score (CISS) will follow a clinimetric approach [12, 13]. Items will be selected through reviewing 17 existing clinical severity indices commonly used in studies for UC and CD (Table 1). To ensure the selected items are applicable to patients with IBD, a focus group of IBD specialists, statisticians and methodologists will review these items and ensure good face and content validity. The CISS will assess the acute and chronic severity of IBD. It will have supplementary questions for perianal disease (to be used when applicable). The CISS will be the first clinical severity index to include all presentations of patients with IBD in one single index.

Recruitment:

This is a prospective multi-centre study which will be carried out over a 3 year period. We will recruit patients with Ulcerative colitis (UC) or Crohn's disease (CD). Patients' medical records will be reviewed to confirm their eligibility as below:

Inclusion criteria:

1. Confirmed diagnosis of UC, Crohn's disease or indeterminate colitis
2. Age 18 years and above
3. Not in a vulnerable group (such as people with mental illness or memory problems, learning difficulties, or physical disabilities)
4. Able to consent.

Exclusion criteria:

1. Patients without a definite diagnosis of UC, Crohn's disease or indeterminate colitis
2. Age less than 18 years
3. Patients within a vulnerable group (such as people with mental illness or memory problems, learning difficulties, or physical disabilities)
4. Unable to consent

If patients meet the inclusion criteria, they will be invited to participate in the study when they attend outpatients or are admitted to hospital. Patients will be asked to give written consent following an oral and written explanation of the study.

The long version of Crohn's and Colitis Quality of life (CCQ) questionnaire will be completed by patients while they are in hospital, in outpatients or at home. Patients will also complete the generic Short Form 12 (SF12) [14] and EuroQoL (EQ5D) [15] questionnaires. They will be asked to complete the same questionnaires within 6 weeks after the initial completion to check test-retest reliability and responsiveness.

The clinical IBD severity score (CISS) will be recorded by the health care professionals when reviewing patients in clinic or on the ward. CISS will be recorded again within 6 weeks after the initial completion in order to check CISS test-retest reliability and responsiveness.

Sample size:

When validating a questionnaire it is important that the sample used is representative of the population in which the instrument is to be used. There are no general criteria for the required sample size in a validation study [13], which is typically based on the assumption that the number of respondents should exceed the number of items in the questionnaire by at least a factor of three [22]. Some authors suggest that rather than the overall sample size it is the ratio of subjects to items that is important and recommends a 10 to 1 ratio for each item [23]. We anticipate the CISS will have 17 different items and the CCQ will have 32 different items. We will therefore aim to recruit a minimum of 170 patients and 320 patients for the validation study of initial versions of CISS and CCQ respectively.

Psychometric analysis:

Data will be analysed using the Statistical Package for Social Sciences (SPSS) version 19 licensed for Swansea University. The main components of psychometric analysis will be:

1. **Internal consistency**

The internal consistency is a measure of reliability. It measures the degree of correlation between different items in the scale. Internal consistency will be assessed by item-total correlations and Cronbach α. Items with item total correlation below 0.2 or more than 0.8 will be rejected [12,13] as they add little information to the scale. Items will also be considered for rejection if more than 80% or less than 20% of patients gave the same response because they

won't be able to differentiate different levels of severity. Items that are ambiguous or found difficult to be answered will be considered for removal or re-wording. Cronbach α of the resulting scale should be > 0.7 [13]. Item discrimination power which is the ability of items to discriminate between patients with different level of severity should be >0.4 [13] otherwise it will be considered for rejection. We will carry out stepwise regression of the total scores on the individual items and will select the items that represent 95% of the variation in the scores to produce short versions of the CCQ and CISS [13].

2. Validity

Construct validity refers to the correlation of the scale with other instruments that are believed to assess the same attribute with high degrees of validity and reliability [13]. It is commonly measured using Pearson correlation coefficient (*r*). Construct validity will be accepted if Pearson correlation is 0.4 – 0.8 [12, 13]. Lower correlations mean either one of the tests has low validity or the two tests are measuring different phenomena while high correlations means the two tests are very similar and the new scale is not needed. Construct validity of CCQ will be assessed using Short Form 12 (SF12) [14] and EuroQoL (EQ5D) [15]. Construct validity of CISS will be checked using biochemical markers: C-reactive protein, white cell count, haemoglobin, albumin and clinical indices: Harvey Bradshaw index [16] (for Crohn's disease), Simple clinical colitis activity index [17] (for Ulcerative colitis) and perianal disease activity index [18] (for perianal Crohn's disease). When patients undergo endoscopy the following endoscopic indices will be recorded: Mayo clinic score [19], Rachmilewitz scores [20] in UC and simple endoscopic score [21] in CD.

3. Test-retest reliability or reproducibility

Reproducibility is used to assess reliability of the test applied on two occasions. To measure reproducibility, CCQ and CISS will be administered to 20% of patients in two occasions. There should be no overall change in their clinical condition between these two intervals. For CCQ, patients will be asked if their health has changed since they last filled the questionnaires. For CISS, we will use physician global assessment to assess if patients' conditions have changed or not. Patients with no change will be included in the reproducibility analysis using intra-class correlation coefficient. For practical reasons, we will allow a maximum of 6 weeks after the first assessment or since the first questionnaire was completed. A value of intra-class correlation of 0.75 [12, 13] will be accepted.

4. **Responsiveness:**

Responsiveness is the ability to detect change. This will be computed by applying CCQ and CISS to 20% of patients in two occasions. For CCQ, patients will be asked if their health has changed since they last filled the questionnaires. For CISS, we will use physician global assessment to assess if patients' conditions have changed or not. Patients whose clinical conditions have changed will be included in the responsiveness analysis using the responsiveness ratio. Responsiveness ratio will be calculated by dividing the mean change in scores for patients who reported a change with the standard deviation of the scores of those who remained stable [13]. A ratio more than 0.5 will be accepted [12,13]. For practical reasons, we will allow a maximum of 6 weeks after the first assessment or since the first questionnaire was completed.

5. **Inter-Observer Reliability:**

This is a measure of reliability to assess the degree of consistency between different observers. We will check the inter-observer reliability of CISS on 20% of patients using inter-class correlation. Two observers will use CISS to assess the same group of patients. We will divide the patients into 2 groups. First group will be assessed by a physician and a specialist nurse while the second group will be assessed by two physicians. A correlation of $>$ 0.75 will be acceptable [13].

Ethics and dissemination:

This study has been approved by the South East Wales Research Ethics Committee (Reference 11/WA/0239). NHS code of confidentiality and Data protection will be adhered to. Once patients are identified, all personal details will be anonymised. Only study related staff will have access to the data. Access will be permitted to appropriately qualified personnel and in accordance with the data protection Act 1998. All data acquisition, storage and transmission will comply with Data Protection Act.

We are committed to publishing our results as widely as possible in peer reviewed journals and to ensuring that appropriate recognition is given to everyone who works on the study.

Authors' contributions: LA is the chief investigator of the study. He contributed in writing the protocol, designing the questionnaires, data analysis and analysis. JGW and HH contributed to designing the questionnaires, all drafts of the protocol and data analysis.

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Competing interests: None.

Appendices:

Table 1: The commonly used clinical severity indices in literature

Ulcerative Colitis:

1. Truelove and Witts severity index [24]
2. Powell Tuck index [25]
3. Simple clinical colitis severity index [17]
4. Lichtiger score [26]
5. Clinical Activity Index (CAI) [20]
6. Physician global assessment [27]
7. Improvement based on individual symptom score [28]
8. Ulcerative colitis clinical severity score [29]
9. Seo Score [30]
10. Mayo Clinic activity score [19]

Crohn's disease:

1. Crohn's disease activity index [31]
2. Harvey Bradshaw index [16]
3. Van Hees index [32]
4. The Cape Town Index [33]
5. Fistula Drainage assessment [34]
6. Perianal Disease Activity Index (PDAI) [35]
7. Perianal Crohn's disease Activity Index (PCDAI) [18]

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IBD has a great impact on the quality of life as it is not curable and follows an unpredictable relapsing and remitting course with significant variation in the pattern and complexity of symptoms that may affect each patient, sometimes leading to hospital admission, surgery and bowel resection, which may leave the patient with a stoma. There are several specific HRQoL measurement tools for patients with inflammatory bowel disease[7, 8, and 9]. However, all of them have been designed for use in the outpatient setting with stable patients and there is no

HRQoL instrument that is validated for use both in the community and by patients who are acutely ill, have a stoma or perianal disease.

In clinical practice, assessing disease severity is an important part of IBD management and a standardized and quantitative evaluation of the severity of IBD is needed for the registry. Due to the varied presentations of IBD, a number of clinical indices have been put forward using different parameters which are based on different principles [10, 11]. Currently available disease severity indices measure disease severity at a single point of time rather than over a longer time period which is an important outcome to assess quality of care. Therefore, a new index that assesses the chronic severity of IBD over a long period of time is needed. A recently reported disability measurement tool for patients with IBD has good correlation with other quality of life and disease severity tools, but has not been validated on acutely unwell patients, only those seen in outpatients [12]. An instrument has been developed to assess the cumulative bowel damage in Crohn's disease but this index is specific for Crohn's disease and requires imaging reports for completion[13]. In order to be widely utilised and generalisable, the index should include as few items as possible which are easily obtainable in any clinical setting and applicable to the majority of patients. An index should also possess the required psychometric properties such as validity and reliability [14,15]. In IBD, there are several different disease severity indices available[10, 11]. However, none of them have been properly validated. Therefore, for a successful IBD registry, there is a need for a short yet reliable and valid severity score index to assess response to treatment and to detect early relapse for all types and presentations of IBD.

Aim:

The aim of the study is to develop valid and reliable HRQoL and disease severity measurement tools that are suitable for use with patients at any stage of their IBD. These tools

will be easily recorded at the point of care to support their use for a registry of patients with IBD.

Objectives of the study:

1. To validate a HRQoL questionnaire (Crohn's and Colitis Quality of Life (CCQ) questionnaire) and derive a short form (Short CCQ) that is suitable for acute and stable patients with IBD and covers patients with a stoma or fistula.

2. To validate a single clinical severity index (Clinical IBD severity index (CISS)) and derive a short form that is suitable for all types and presentations of IBD.

Methods and analysis:

Developing the outcome measures:

1. The Crohn's and Colitis Health related quality of life questionnaire

The initial version of the Crohn's and Colitis Health related quality of life questionnaire (CCQ) will be based on the UK Inflammatory Bowel Disease Questionnaire (UK IBDQ) [9] that was developed and validated in 2000. An extensive literature review will be carried out to identify supplementary items to reflect the wide range and frequency of symptoms of IBD when patients are seen as outpatients, inpatients, with perianal disease and with a stoma. The first draft of CCQ will be an inclusive as possible to cover all patients with IBD. We will validate the CCQ with a wider group of patients to include patients with both Crohn's disease (CD) and Ulcerative colitis (UC) as well as patients with a stoma and Crohn's perianal disease. The questionnaire will be examined by IBD specialists, methodologists and statisticians to ensure good face and content validity of the items. To ensure that the resulting questionnaire is clear to patients, we will conduct a feasibility study, asking a small sample of patients to complete the questionnaires. Quality of life will thus be presented as a simple score that will be derived from items completed by patients with different IBD phenotypes in a

broad spectrum of settings. The score will enable monitoring over time and comparative assessment across different UK locations.

2. The Clinical IBD Severity Score (CISS)

The development of Clinical IBD Severity Score (CISS) will follow a clinimetric approach [14,15.] Items will be selected through reviewing 17 existing clinical severity indices commonly used in studies for UC and CD (Table 1). To ensure the selected items are applicable to patients with IBD, a focus group of at least 6 IBD specialists from different UK hospitals , statisticians and methodologists will review these items and ensure good face and content validity. The CISS will assess the acute and chronic severity of IBD. It will have supplementary questions for perianal disease (to be used when applicable). The CISS will be the first clinical severity index to include all presentations of patients with IBD in one single index.

Recruitment:

This is a prospective multi-centre study which will be carried out over a 3 year period. Sites will be invited and patients' will be recruited over a 24 month period Data analysis and production of the final version of the questionnaires will be carried out in the following 12 months We will recruit patients with Ulcerative colitis (UC) or Crohn's disease (CD). Invitations will be sent to teaching and general district hospitals across the UK. We will aim to recruit at least 4 different UK sites. Patients' medical records will be reviewed to confirm their eligibility as below:

Inclusion criteria:

1. Confirmed diagnosis of UC, Crohn's disease or indeterminate colitis
2. Age 18 years and above
3. Not in a vulnerable group (such as people with mental illness or memory problems, learning difficulties, or physical disabilities)

4. Able to consent.

Exclusion criteria:

1. Patients without a definite diagnosis of UC, Crohn's disease or indeterminate colitis
2. Age less than 18 years
3. Patients within a vulnerable group (such as people with mental illness or memory problems, learning difficulties, or physical disabilities)
4. Unable to consent

If patients meet the inclusion criteria, they will be invited to participate in the study when they attend outpatients or are admitted to hospital. Patients will be asked to give written consent following an oral and written explanation of the study.

The long version of Crohn's and Colitis Quality of life (CCQ) questionnaire will be completed by patients while they are in hospital, in outpatients or at home. Patients will also complete the generic Short Form 12 (SF12) [16] and EuroQoL (EQ5D) [17] questionnaires. They will be asked to complete the same questionnaires within 6 weeks after the initial completion to check test-retest reliability and responsiveness.

The clinical IBD severity score (CISS) will be recorded by the health care professionals when reviewing patients in clinic or on the ward. CISS will be recorded again within 6 weeks after the initial completion in order to check CISS test-retest reliability and responsiveness.

Sample size:

When validating a questionnaire it is important that the sample used is representative of the population in which the instrument is to be used. There are no general criteria for the required sample size in a validation study [15], which is typically based on the assumption that the number of respondents should exceed the number of items in the questionnaire by at least a

factor of three [22]. Some authors suggest that rather than the overall sample size it is the ratio of subjects to items that is important and recommends a 10 to 1 ratio for each item [25]. We anticipate the CISS will have 17 different items and the CCQ will have 32 different items. We will therefore aim to recruit a minimum of 170 patients and 320 patients for the validation study of initial versions of CISS and CCQ respectively.

Psychometric analysis:

Data will be analysed using the Statistical Package for Social Sciences (SPSS) version 19 licensed for Swansea University. The main components of psychometric analysis will be:

1. **Internal consistency**

The internal consistency is a measure of reliability. It measures the degree of correlation between different items in the scale. Internal consistency will be assessed by item-total correlations and Cronbach α. Items with item total correlation below 0.2 or more than 0.8 will be rejected [14,15] as they add little information to the scale. Items will also be considered for rejection if more than 80% or less than 20% of patients gave the same response because they won't be able to differentiate different levels of severity. Items that are ambiguous or found difficult to be answered will be considered for removal or re-wording. Cronbach α of the resulting scale should be > 0.7 [15]. Item discrimination power which is the ability of items to discriminate between patients with different level of severity should be >0.4 [15] otherwise it will be considered for rejection. We will carry out stepwise regression of the total scores on the individual items and will select the items that represent 95% of the variation in the scores to produce short versions of the CCQ and CISS [15].

2. Validity

Construct validity refers to the correlation of the scale with other instruments that are believed to assess the same attribute with high degrees of validity and reliability [13]. It is commonly measured using Pearson correlation coefficient (*r*). Construct validity will be accepted if Pearson correlation is 0.4 – 0.8 [14,15]. Lower correlations mean either one of the tests has low validity or the two tests are measuring different phenomena while high correlations means the two tests are very similar and the new scale is not needed. Construct validity of CCQ will be assessed using Short Form 12 (SF12) [16] and EuroQoL (EQ5D) [17]. Construct validity of CISS will be checked using biochemical markers: C-reactive protein, white cell count, haemoglobin, albumin and clinical indices: Harvey Bradshaw index [18] (for Crohn's disease), Simple clinical colitis activity index [19] (for Ulcerative colitis) and perianal disease activity index [20] (for perianal Crohn's disease). These clinical indices will be selected because they are easy to use and widely cited [10,11] in the literature. When patients undergo endoscopy the following endoscopic indices will be recorded: Mayo clinic score [21], Rachmilewitz scores [22] in UC and simple endoscopic score [23] in CD.

3. Test-retest reliability or reproducibility

Reproducibility is used to assess reliability of the test applied on two occasions. To measure reproducibility, CCQ and CISS will be administered to 20% of patients in two occasions. There should be no overall change in their clinical condition between these two intervals. For CCQ, patients will be asked if their health has changed since they last filled the questionnaires. For CISS, we will use physician global assessment to assess if patients' conditions have changed or not. Patients with no change will be included in the reproducibility analysis using intra-class correlation coefficient. For practical reasons, we will allow a period of 2-6 weeks after the first assessment or since the first questionnaire was

completed. Previous studies have illustrated that a period of less than 2 weeks is not reliable as patients might remember their answers and select them again [14,15]. Therefore we expect to include patients with quiescent to moderate IBD for the reproducibility analysis because patients with severe IBD will more likely have their disease changed or have surgery within 2 weeks. A value of intra-class correlation of 0.75 [14,15] will be accepted.

4. Responsiveness:

Responsiveness is the ability to detect change. This will be computed by applying CCQ and CISS to 20% of patients in two occasions. For CCQ, patients will be asked if their health has changed since they last filled the questionnaires. For CISS, we will use physician global assessment to assess if patients' conditions have changed or not. Patients whose clinical conditions have changed will be included in the responsiveness analysis using the responsiveness ratio. Responsiveness ratio will be calculated by dividing the mean change in scores for patients who reported a change with the standard deviation of the scores of those who remained stable [15]. A ratio more than 0.5 will be accepted [14,15]. For practical reasons, we will allow a maximum of 6 weeks after the first assessment or since the first questionnaire was completed.

5. Inter-Observer Reliability:

This is a measure of reliability to assess the degree of consistency between different observers. We will check the inter-observer reliability of CISS on 20% of patients using inter-class correlation. Two observers will use CISS to assess the same group of patients. We will divide the patients into 2 groups. First group will be assessed by a physician and a specialist nurse while the second group will be assessed by two physicians. A correlation of > 0.75 will be acceptable [15].

Ethics and dissemination:

This study has been approved by the South East Wales Research Ethics Committee (Reference 11/WA/0239). NHS code of confidentiality and Data protection will be adhered to. Once patients are identified, all personal details will be anonymised. Only study related staff will have access to the data. Access will be permitted to appropriately qualified personnel and in accordance with the data protection Act 1998. All data acquisition, storage and transmission will comply with Data Protection Act.

We are committed to publishing our results as widely as possible in peer reviewed journals and to ensuring that appropriate recognition is given to everyone who works on the study.

Authors' contributions: LA is the chief investigator of the study. He contributed in writing the protocol, designing the questionnaires, data analysis and analysis. JGW and HH contributed to designing the questionnaires, all drafts of the protocol and data analysis.

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Competing interests: None.

Appendices:

Table 1: The commonly used clinical severity indices in literature

Ulcerative Colitis:

1. Truelove and Witts severity index [26]
2. Powell Tuck index [27]
3. Simple clinical colitis severity index [19]
4. Lichtiger score [28]
5. Clinical Activity Index (CAI) [22]
6. Physician global assessment [29]
7. Improvement based on individual symptom score [30]
8. Ulcerative colitis clinical severity score [31]
9. Seo Score [32]
10. Mayo Clinic activity score [21]

Crohn's disease:

1. Crohn's disease activity index [33]
2. Harvey Bradshaw index [18]
3. Van Hees index [34]
4. The Cape Town Index [35]
5. Fistula Drainage assessment [36]
6. Perianal Disease Activity Index (PDAI) [37]
7. Perianal Crohn's disease Activity Index (PCDAI) [20]

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Protocol for a prospective multicentre cohort study to develop and validate two new outcome measures for patients with inflammatory bowel disease.

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Abstract:

Introduction: Most of the health related quality of life (HRQoL) measures for patients with inflammatory bowel disease (IBD) were designed to be used in outpatient settings and are, therefore, not suitable for use in acute inpatient settings. None of the currently used clinical severity indices for patients with IBD have been properly validated. The aim of this study is to describe the development of a new health related quality of life questionnaire and a clinical severity index for patients with ulcerative colitis or Crohn's disease that are short , valid and suitable at any stage of their disease. These new outcome measurement tools will be easily used at the point of care, and invaluable monitoring tools for clinical care, audit and research.

Methods and analysis: This is a prospective multi-site validation study of two new outcome measures, the Crohn's and Colitis quality of life (CCQ) questionnaire and the Clinical IBD severity score (CISS). We plan to recruit patients with ulcerative colitis or Crohn's disease. Questionnaire items will be selected through extensive literature review and a focus group involving patients, methodologists, statisticians and IBD specialists. The CCQ questionnaire will be completed by patients attending IBD clinics, having endoscopy procedures or when admitted to hospital. The CISS will be completed by clinicians while assessing patients with IBD. Psychometric analysis will be carried out to test the validity and the reliability of the questionnaires and determine the potential to produce shorter versions of CISS and CCQ. The construct validity of the CCQ will be tested against short form-12 (SF12) and the European Quality of Life Five Dimensions (EQ5D). The construct validity of CISS will be tested against biochemical markers, clinical and endoscopic indices to assess severity.

Ethics: This study was approved by the South East Wales Research Ethics Committee (Ref 11/WA/0239).

Article summary:

Article focus:

- None of the currently used clinical severity indices for patients with inflammatory bowel disease (IBD) have been properly validated.
- Most of the health related quality of life (HRQoL) measures for patients with IBD have been designed for use in outpatient settings and are, therefore, not suitable for use in acute inpatient settings
- This article describes the protocol for a prospective multi-site validation study of two new outcome measures; the Crohn's and Colitis Health related quality of life (CCQ) questionnaire and the Clinical IBD severity score (CISS).

Key measures:

- The main focus of the article is the development and validation of two outcome measures to assess the quality of life and disease severity of patients with IBD.
- This article provides an insight into the methods used to develop and validate new outcome measures which can applied to any disease.

Strength and limitations of this study:

- The CISS will be the first fully validated clinical severity index for patients with IBD.
- The CCQ will be the first health related quality of life tool that will be applicable to all types and presentations of IBD.
- It may be difficult to recruit adequate numbers of patients with less common presentations of IBD like perianal Crohn's disease or patients with extra-intestinal manifestations.

Introduction:

Inflammatory bowel disease (IBD) affects approximately one person in every 250 in the United Kingdom population[1]. The cost of IBD to the NHS has been estimated at about £720 million per annum, based on the prevalence and an average cost of £3,000 per year per patient [2]. The lifetime medical costs associated with the care of IBD are comparable with major chronic diseases such as diabetes mellitus or cancer [2]. Anti Tumour Necrosis factor α (Anti TNF-α) drugs are new and effective biological treatments for both ulcerative colitis [3] and Crohn's disease [4] but long-term outcomes are still unknown and there are a number of safety issues [5]. Therefore, the National Institute for Health and Clinical Excellence (NICE) has recommended the establishment of a Registry for patients with IBD treated with biological therapy [6]. Assessment of response to treatment will require measurement of both HRQoL and disease severity.

HRQoL questionnaires are often employed as measures of health status and are important outcome measures in clinical trials. They should form an integral part of any outcome monitoring efforts but are often omitted from large scale registries because of constraints on the amount of data these registries can collect. To facilitate adoption of HRQoL measures in large IBD registries, it is important to develop instruments which are short and easy to complete, yet valid, reliable and applicable to all IBD patients.

IBD has a great impact on the quality of life as it is not curable and follows an unpredictable relapsing and remitting course with significant variation in the pattern and complexity of symptoms that may affect each patient, sometimes leading to hospital admission, surgery and bowel resection, which may leave the patient with a stoma. There are several specific HRQoL measurement tools for patients with inflammatory bowel disease[7, 8, and 9]. However, all of them have been designed for use in the outpatient setting with stable patients and there is no

HRQoL instrument that is validated for use both in the community and by patients who are acutely ill, have a stoma or perianal disease.

In clinical practice, assessing disease severity is an important part of IBD management and a standardized and quantitative evaluation of the severity of IBD is needed for the registry. Due to the varied presentations of IBD, a number of clinical indices have been put forward using different parameters which are based on different principles [10, 11]. Currently available disease severity indices measure disease severity at a single point of time rather than over a longer time period which is an important outcome to assess quality of care. Therefore, a new index that assesses the chronic severity of IBD over a long period of time is needed. A recently reported disability measurement tool for patients with IBD has good correlation with other quality of life and disease severity tools, but has not been validated on acutely unwell patients, only those seen in outpatients [12]. An instrument has been developed to assess the cumulative bowel damage in Crohn's disease but this index is specific for Crohn's disease and requires imaging reports for completion[13]. In order to be widely utilised and generalisable, the index should include as few items as possible which are easily obtainable in any clinical setting and applicable to the majority of patients. An index should also possess the required psychometric properties such as validity and reliability [14,15]. In IBD, there are several different disease severity indices available[10, 11]. However, none of them have been properly validated. Therefore, for a successful IBD registry, there is a need for a short yet reliable and valid severity score index to assess response to treatment and to detect early relapse for all types and presentations of IBD.

Aim:

The aim of the study is to develop valid and reliable HRQoL and disease severity measurement tools that are suitable for use with patients at any stage of their IBD. These tools

will be easily recorded at the point of care to support their use for a registry of patients with IBD.

Objectives of the study:

1. To validate a HRQoL questionnaire (Crohn's and Colitis Quality of Life (CCQ) questionnaire) and derive a short form (Short CCQ) that is suitable for acute and stable patients with IBD and covers patients with a stoma or fistula.

2. To validate a single clinical severity index (Clinical IBD severity index (CISS)) and derive a short form that is suitable for all types and presentations of IBD.

Methods and analysis:

Developing the outcome measures:

1. The Crohn's and Colitis Health related quality of life questionnaire

The initial version of the Crohn's and Colitis Health related quality of life questionnaire (CCQ) will be based on the UK Inflammatory Bowel Disease Questionnaire (UK IBDQ) [9] that was developed and validated in 2000. An extensive literature review will be carried out to identify supplementary items to reflect the wide range and frequency of symptoms of IBD when patients are seen as outpatients, inpatients, with perianal disease and with a stoma. The first draft of CCQ will be an inclusive as possible to cover all patients with IBD. We will validate the CCQ with a wider group of patients to include patients with both Crohn's disease (CD) and Ulcerative colitis (UC) as well as patients with a stoma and Crohn's perianal disease. The questionnaire will be examined by IBD specialists, methodologists and statisticians to ensure good face and content validity of the items. To ensure that the resulting questionnaire is clear to patients, we will conduct a feasibility study, asking a small sample of patients to complete the questionnaires. Quality of life will thus be presented as a simple score that will be derived from items completed by patients with different IBD phenotypes in a

broad spectrum of settings. The score will enable monitoring over time and comparative assessment across different UK locations.

2. The Clinical IBD Severity Score (CISS)

The development of Clinical IBD Severity Score (CISS) will follow a clinimetric approach [14,15]. Items will be selected through reviewing 17 existing clinical severity indices commonly used in studies for UC and CD (Table 1). To ensure the selected items are applicable to patients with IBD, a focus group of at least 6 IBD specialists from different UK hospitals, statisticians and methodologists will review these items and ensure good face and content validity. The CISS will assess the acute and chronic severity of IBD. It will have supplementary questions for perianal disease (to be used when applicable). The CISS will be the first clinical severity index to include all presentations of patients with IBD in one single index.

Recruitment:

This is a prospective multi-centre study which will be carried out over a 3 year period. Sites will be invited and patients' will be recruited over a 24 month period Data analysis and production of the final version of the questionnaires will be carried out in the following 12 months. We will recruit patients with Ulcerative colitis (UC) or Crohn's disease (CD). Invitations will be sent to teaching and general district hospitals across the UK. We will aim to recruit at least 4 different UK sites. Patients' medical records will be reviewed to confirm their eligibility as below:

Inclusion criteria:

1. Confirmed diagnosis of UC, Crohn's disease or indeterminate colitis
2. Age 18 years and above
3. Not in a vulnerable group (such as people with mental illness or memory problems, learning difficulties, or physical disabilities)

4. Able to consent.

Exclusion criteria:

1. Patients without a definite diagnosis of UC, Crohn's disease or indeterminate colitis
2. Age less than 18 years
3. Patients within a vulnerable group (such as people with mental illness or memory problems, learning difficulties, or physical disabilities)
4. Unable to consent

If patients meet the inclusion criteria, they will be invited to participate in the study when they attend outpatients or are admitted to hospital. Patients will be asked to give written consent following an oral and written explanation of the study.

The long version of Crohn's and Colitis Quality of life (CCQ) questionnaire will be completed by patients while they are in hospital, in outpatients or at home. Patients will also complete the generic Short Form 12 (SF12) [16] and EuroQoL (EQ5D) [17] questionnaires. They will be asked to complete the same questionnaires within 6 weeks after the initial completion to check test-retest reliability and responsiveness.

The clinical IBD severity score (CISS) will be recorded by the health care professionals when reviewing patients in clinic or on the ward. CISS will be recorded again in 2-6 weeks after the initial completion in order to check CISS test-retest reliability and responsiveness.

Sample size:

When validating a questionnaire it is important that the sample used is representative of the population in which the instrument is to be used. There are no general criteria for the required sample size in a validation study [15], which is typically based on the assumption that the number of respondents should exceed the number of items in the questionnaire by at least a

factor of three [22]. Some authors suggest that rather than the overall sample size it is the ratio of subjects to items that is important and recommends a 10 to 1 ratio for each item [25]. We anticipate the CISS will have 17 different items and the CCQ will have 32 different items. We will therefore aim to recruit a minimum of 170 patients and 320 patients for the validation study of initial versions of CISS and CCQ respectively.

Psychometric analysis:

Data will be analysed using the Statistical Package for Social Sciences (SPSS) version 19 licensed for Swansea University. The main components of psychometric analysis will be:

1. **Internal consistency**

The internal consistency is a measure of reliability. It measures the degree of correlation between different items in the scale. Internal consistency will be assessed by item-total correlations and Cronbach α. Items with item total correlation below 0.2 or more than 0.8 will be rejected [14,15] as they add little information to the scale. Items will also be considered for rejection if more than 80% or less than 20% of patients gave the same response because they won't be able to differentiate different levels of severity. Items that are ambiguous or found difficult to be answered will be considered for removal or re-wording. Cronbach α of the resulting scale should be > 0.7 [15]. Item discrimination power which is the ability of items to discriminate between patients with different level of severity should be >0.4 [15] otherwise it will be considered for rejection. We will carry out stepwise regression of the total scores on the individual items and will select the items that represent 95% of the variation in the scores to produce short versions of the CCQ and CISS [15].

2. Validity

Construct validity refers to the correlation of the scale with other instruments that are believed to assess the same attribute with high degrees of validity and reliability [13]. It is commonly measured using Pearson correlation coefficient (*r*). Construct validity will be accepted if Pearson correlation is 0.4 – 0.8 [14,15]. Lower correlations mean either one of the tests has low validity or the two tests are measuring different phenomena while high correlations means the two tests are very similar and the new scale is not needed. Construct validity of CCQ will be assessed using Short Form 12 (SF12) [16] and EuroQoL (EQ5D) [17]. Construct validity of CISS will be checked using biochemical markers: C-reactive protein, white cell count, haemoglobin, albumin and clinical indices: Harvey Bradshaw index [18] (for Crohn's disease), Simple clinical colitis activity index [19] (for Ulcerative colitis) and perianal disease activity index [20] (for perianal Crohn's disease). These clinical indices will be selected because they are easy to use and widely cited [10,11] in the literature. When patients undergo endoscopy the following endoscopic indices will be recorded: Mayo clinic score [21], Rachmilewitz scores [22] in UC and simple endoscopic score [23] in CD.

3. Test-retest reliability or reproducibility

Reproducibility is used to assess reliability of the test applied on two occasions. To measure reproducibility, CCQ and CISS will be administered to 20% of patients in two occasions. There should be no overall change in their clinical condition between these two intervals. For CCQ, patients will be asked if their health has changed since they last filled the questionnaires. For CISS, we will use physician global assessment to assess if patients' conditions have changed or not. Patients with no change will be included in the reproducibility analysis using intra-class correlation coefficient. For practical reasons, we will allow a period of 2-6 weeks after the first assessment or since the first questionnaire was

completed. Previous studies have illustrated that a period of less than 2 weeks is not reliable as patients might remember their answers and select them again [14,15]. Therefore we expect to include patients with quiescent to moderate IBD for the reproducibility analysis because patients with severe IBD will more likely have their disease changed or have surgery within 2 weeks. A value of intra-class correlation of 0.75 [14,15] will be accepted.

4. Responsiveness:

Responsiveness is the ability to detect change. This will be computed by applying CCQ and CISS to 20% of patients in two occasions. For CCQ, patients will be asked if their health has changed since they last filled the questionnaires. For CISS, we will use physician global assessment to assess if patients' conditions have changed or not. Patients whose clinical conditions have changed will be included in the responsiveness analysis using the responsiveness ratio. Responsiveness ratio will be calculated by dividing the mean change in scores for patients who reported a change with the standard deviation of the scores of those who remained stable [15]. A ratio more than 0.5 will be accepted [14,15]. For practical reasons, we will allow a maximum of 6 weeks after the first assessment or since the first questionnaire was completed.

5. Inter-Observer Reliability:

This is a measure of reliability to assess the degree of consistency between different observers. We will check the inter-observer reliability of CISS on 20% of patients using inter-class correlation. Two observers will use CISS to assess the same group of patients. We will divide the patients into 2 groups. First group will be assessed by a physician and a specialist nurse while the second group will be assessed by two physicians. A correlation of > 0.75 will be acceptable [15].

Ethics and dissemination:

This study has been approved by the South East Wales Research Ethics Committee (Reference 11/WA/0239). NHS code of confidentiality and Data protection will be adhered to. Once patients are identified, all personal details will be anonymised. Only study related staff will have access to the data. Access will be permitted to appropriately qualified personnel and in accordance with the data protection Act 1998. All data acquisition, storage and transmission will comply with Data Protection Act.

We are committed to publishing our results as widely as possible in peer reviewed journals and to ensuring that appropriate recognition is given to everyone who works on the study.

Authors' contributions: LA is the chief investigator of the study. He contributed in writing the protocol, designing the questionnaires, data analysis and analysis. JGW and HH contributed to designing the questionnaires, all drafts of the protocol and data analysis.

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Competing interests: None.

Appendices:

Table 1: The commonly used clinical severity indices in literature

Ulcerative Colitis:

1. Truelove and Witts severity index [26]
2. Powell Tuck index [27]
3. Simple clinical colitis severity index [19]
4. Lichtiger score [28]
5. Clinical Activity Index (CAI) [22]
6. Physician global assessment [29]
7. Improvement based on individual symptom score [30]
8. Ulcerative colitis clinical severity score [31]
9. Seo Score [32]
10. Mayo Clinic activity score [21]

Crohn's disease:

1. Crohn's disease activity index [33]
2. Harvey Bradshaw index [18]
3. Van Hees index [34]
4. The Cape Town Index [35]
5. Fistula Drainage assessment [36]
6. Perianal Disease Activity Index (PDAI) [37]
7. Perianal Crohn's disease Activity Index (PCDAI) [20]

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