**Title: International Consensus of the Management of Benign Barrett's**

Benign Barrett's and CAncer Taskforce **'BoB CAT'** consensus group

This is an inclusive international systematic evidence base group which aims to use workshops and iterative web based voting rounds to identify factors which can be used to stratify risk in benign Barrett's esophagus.

Questions will be formulated in a clear PICO format (Population, Intervention, Comparator group and Outcome) so that a GRADE quality assessment of the evidence can be performed.

The group will include representatives of all major international professional and patient organizations so that the document has global relevance.

**Endorsed and Funded to date by**

International Society of Diseases of the Esophagus ISDE (approved) $5,000, received

Oesophageal Charity Fund of Ireland OCF, (donation from OCF, which is an Irish charity) (approved) $6,200, received

Fight Oesophageal Reflux Together FORT (approved) $7,500, received

Association of Upper GI Surgeons AUGIS (approved) $1,500, received

British Society of Gastroenterology (approved) $5,000, received

German Gastroenterology Society (approved), funds pending

American Gastroenterology Association (approved) $2,500, received

American College of Gastroenterology (approved), funds pending

Canadian Association of Gastroenterology (formal application sought)

Deutschen Gesellschaft für Verdauungs und Stoffwechselkrankheiten (DGVS) (approved) €1,000

**Endorsement only**

American College of Gastroenterology (approved)

International Working Group for Columnar Oesophagus (approved)

European Society of Thoracic Surgeons (approved)

World Gastroenterology Organisation (approved)

All organizations were asked to contribute $5000 US to the project. All contributing organizations will be acknowledged in the final document and all aspects of the project will be open to scrutiny and ownership. In the case of one organization making a larger donation this will lead to this organization being given greater recognition in the final iteration of the outcomes.

**2. Overview of the Clinical Need**

The dogma suggests that Barrett's related adenocarcinoma develops from chronic esophagitis, through benign Barrett's, then stage of dysplasia and ultimately invasive cancer. However the precise relationship between GORD, BO and subsequent cancer is unclear. Most patients are diagnosed with BO because they had heartburn and were referred to a specialist. Many patients in surveillance programs are not fully aware of the risk /benefits of surveillance. Estimates from epidemiological studies suggest that Barrett's esophagus progresses to cancer in 1-5% of cases. In the remaining 95% there is no cancer risk however these patients are subjected to unnecessary endoscopy and anxiety. The incidence of esophageal adenocarcinoma in the UK is one of the highest in the world, such that it is more common than gastric cancer.

Current evidence of BE management

Evidence suggests that establishing a valid disease register specific for Barrett's esophagus with dedicated endoscopists performing surveillance according to strict protocols results in an better adherence to the planned surveillance interval (increased from 17% to 92%) and improvement in the collection of sufficient biopsies (increased from 45% to 83%). Long term follow-up for high risk BO with appropriate endoscopic imaging should be delivered by tertiary level super specialist centers. High dose PPIs and anti-reflux surgery for underlying symptoms of GORD may be helpful, but awaiting outcomes of trials to determine if there is any reduction in cancer. Current surveillance of BO is not supported by robust evidence based data and much clinical practice falls below best recommendations. Audit has shown that many patients under surveillance have significant co-morbidities which either cause death or prevent curative surgical intervention. Upper GI endoscopy and biopsy remain the gold standard for diagnosis.

There is a need to stratify BE patients into three categories a. No or Low Risk (Green) b. Medium Risk (Yellow) and c. High Risk (Red). While at this stage individualized risk has never been tested prospectively there is enough data to discriminate important epidemiological factors, pathological factors including co-morbidities and principal biomarkers of progression.

In general terms we would hope to indicate broad lifetime risks of progression to adenocarcinoma <1% (No or Low Risk ~ 65% of patients), 1-10% (Medium Risk ~ 30% of patients) and >10% (High Risk ~ 5% of patients).

The purpose of this consensus panel is to combine the best group risk factors from epidemiology, biology and inherited genetics to inform clinical practice.

In addition, there are several new diagnostic and therapeutic technologies that are being used to deal with this condition with an insubstantial evidence base. Management of Barrett's also has great national and international variance in management. The RAND Corporation developed the Delphi consensus method and then modified it further. This process has been used successfully in several gastrointestinal consensus statements. In this regard following on from the success of BAD CAT for high grade dysplasia in Barrett's metaplasia (Gastroenterology 2012 in press) we would like to address the more challenging question of progression in benign Barrett's metaplasia. In particular we would like to identify clinico-pathological, biological and genetic factors which could be used for stratification of the management of benign Barrett's.

**3. Aim/Remit:**

a. To use a systematic evidence base review in iterative steps to produce guidelines for best clinical and cost effective management of benign Barrett's esophagus in prevention of esophageal adenocarcinoma.

b. A second aim will be to identify demographic, endoscopic, pathological and biomarker factors where there is good evidence to provide stratification directly applicable to clinical management.

c. Use these factors prospectively in a predictive and prognostic clinical study with estimated relative risks for each factor

**4. Population and Outcomes**

Population: adults over 18 years with a diagnosis of Barrett's esophagus with either no dysplasia, indefinite dysplasia or low grade dysplasia (esophagitis alone is not included).

Intervention: anti-reflux surgery, endotherapy, proton pump inhibitors, aspirin

Comparator: surveillance or no action

Outcome: What outcomes should be measured for therapy (lack of progression, regression to non-dysplastic or neo-squamous mucosa, 5 year survival and overall survival)?

**5. Mechanism:** to use a Delphi mechanism process to produce iterative changes for producing an evidence based consensus such as done previously for the management of dysplastic Barrett's (BAD CAT) and GERD**.**

Search strategies and selection of studies and formulation of PICO questions

We will produce an informal set of questions, then refine this to define PICO (Population of study, Intervention, Comparator, Outcome) questions for individual topics (see table below, with example of how this could have been done for BAD CAT). The PICO format will help to determine if some questions should be lumped in to larger topics or split in to smaller ones (e.g. it would be possible to lump together all PPIs as a class without the need to separate out on a per drug basis).

We will define outcomes in terms of importance and separate those that are final health outcomes from surrogate (intermediary) outcomes, and how strongly those surrogate outcomes are connected to final patient-important outcomes.

In regards to non-intervention questions (epidemiology and pathology especially): those are usually related to prevalence (or baseline risk), which is important when calculating absolute risk differences (or NNTs) of recommended interventions. Questions of prognosis are similarly connected as they define populations that would be at higher (or lower) risk. Therefore at times we may end up with different recommendations based upon a higher or lower baseline risk

For pathology we will define parameters, (such as 'are more biopsies better than fewer?'), and clearly specify if we are looking at the question from the point of accuracy of diagnosis as the outcome, or outcomes such as survival relating to more aggressive management as a result of changed practice.

We could instead prioritize questions and produce a small number of statements with pooled estimates (for the most important and controversial topics). There may already be systematic reviews such as Cochrane reviews which have already addressed these issues that we could incorporate.

We could produce narrative discussions of the evidence for the other topics. A voting round could be used to narrow down the most important topics.

Example table of PICO format based on BAD CAT questions (produced by Y FY)

| Section | Informal Question (from BADCAT v30v50) | PICO Question | | | | Method. |
|---|---|---|---|---|---|---|
| | | **Population** | **Intervention(s)** | **Comparator** | **Outcome** | |
| **Endoscopy** | Is there an agreed interval that the biopsies be taken to ensure HGD has not progressed or regressed? | Patients with Barrett's Esophagus and HGD on index endoscopy | Repeat EGD with 4 quadrant biopsies in 6 months | 1. 3 months<br>2. 12 months | Esophageal cancer<br>Cost | RCT, obs. studies |
| **Medical Therapy** | Is it known what the evidence is that PPI's can prevent progression of LGD/HGD to cancer in Barrett's? | Patients with Barrett's Esophagus and HGD on index endoscopy | PPI's | Placebo | Esophageal cancer<br>PPI adverse events<br>Cost | RCT |
| **Endoscopic therapies** | Is it known what the endoscopic therapy results are for HGD or T1m: RFA | Patients with Barrett's Esophagus and HGD on index endoscopy | RFA | Sham (surveillance) | Esophageal cancer<br>HGD on f/u<br>EGD(surrogate)<br>Chest pain<br>Esophageal stricture | RCT |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | UGI hemorrhage<br><br>Cost | |

Published papers will be searched by an experienced consultant (please see Appendix 1). This will be done after questions are formulated in detail (PICO formulated). Published and unpublished reports identified by the literature search, will be assessed for eligibility and data will be extracted from evidence tables and summarized either qualitatively or quantitatively, to support evidence based statements which address each question. Internal (methodology flaws of design or bias) and external validity (generalizability) will be assessed in relevant papers. Expert sub groups dealing with the questions (vide infra) will assess the data and provide detailed reports. *(Note, this section revised and edited for clarity, Sept 2012)*

3-5 Key individuals assigned to a working group will be allocated to each of the questions and should prepare a 2 page 1000 word statement along with 10-20 key references.

This may be summarized for a comprehensive final manuscript and shorter length executive summaries for (Dis of Oesophagus/Am J Gastroenterology/ GUT/Gastroenterology)

Working and Consensus group (100-120 people 3-4 for each set of questions): to do literature search and prepare documents and do presentations and vote on the iterations of the writings of the working group to form a consensus.

The group will meet initially at the ISDE in Venice October 2012 to discuss the format, evidence and content of the panels for each group. The first draft iteration will be presented at the DDW in the USA 2013 and final draft of the questions and answers at the BSG in Glasgow June 2013.

Each forum will have members of the core group person presenting the results of the group's agreed-upon statements.

GRADE

We will use GRADE methodology to:

- Determine GRADE PICO Question.
- Determine most important desirable and undesirable outcomes
- Rate quality of evidence (type of evidence, quality, directness, consistency, effect size)
- Determine recommendation (strong/weak) and summarize basis for recommendation

References:

Guyatt G et al. J Clin Epidemiol. 2011 Apr;64(4):395-400. GRADE guidelines: 2. Framing the question and deciding on important outcomes.

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group.
Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians? BMJ. 2008 May 3;336(7651):995-8

**Meta analyses**

We may attempt meta-analysis of some of the biomarker statements and PICO is essential for any question where quantitative data synthesis might be possible. The potential of meta-analyses of biomarkers may prove infeasible but several groups are quoting predictive values from various studies.

**Governance of BoB CAT**

**Membership of the group.**

First all interested parties in esophageal disease from biomarkers, translational medicine, clinical trials, epidemiology, patient advocacy, endoscopy, pathology and even interested clinicians being contacted by current members of the group on an ad hoc basis. Second we will ask the major GI societies to contact the relevant committees to solicit membership. Third we will ask major GI journals to post a short advert requesting membership.

"We would like to invite you to join the International Consensus of the Management of Benign Barrett's (Benign Barrett's and CAncer Taskforce 'BoB CAT' consensus group)

This is an inclusive international systematic evidence base group which aims to use workshops and iterative web based voting rounds to identify factors which can be used to stratify risk in benign Barrett's esophagus. Questions will be formulated in a clear PICO format (population, Intervention, Comparator group and Outcome) so that a GRADE quality assessment of the evidence can be performed.
The group will include representatives of all major international professional and patient organizations so that the document has global relevance (see front page for funding and endorsements).

Please reply by email to Prof Janusz Jankowski (j.a.jankowski@qmul.ac.uk), the convenor of BOB CAT, or Dr Cathy Bennett (info@systematicresearch.co.uk), research co-ordinator, with an indication of your specialty and outline of your interest in working with us."

Inclusion of new members ceased before Round 1 to select and shortlist questions. New members were added after this round, but membership will be finalized before voting on evidence based statements begins in late 2012.as we will begin the voting rounds on the evidence.

**Development and selection of statements**

Members will be requested to select statements for BoB CAT and this process will end in July (date to be decided). We propose having 200 questions and voting on those which are the most clinically relevant. We will choose the top 70-100 statements making sure at least 4 from each discipline e.g. pathology, biomarkers, endoscopy are selected and the highest ranking statements thereafter being selected regardless of topic. The final selection of questions will be

finalized by the core group and may include questions which did not score highly but where there is an urgent need for review of the evidence. This vote commenced 1st October 2012. After this round, accepted questions will be refocused as statements and simplified (new statements may be added at this time at the request of BOB CAT members).

Results of Round 1 Voting: 84 completed, 24 partially completed. See summary page http://mdpub.org/bobcat/

**Voting process**

The voting process will be analogous to BAD CAT and we will use 3 rounds of web based voting to try to get agreement on statements with iterative changes to the evidence and/or phrasing of question to achieve clarity where needed. We may also add similar questions to duplicate responses in an attempt to assess consistency of response.

**Authorship (see Appendix for detailed Authorship Guidelines)**

An authorship Committee, led by Yvonne Romero, Doug Corley, Peter Watson and Giovanni Zaninotto, will review the literature and contact large established groups who have established authorship guidelines (like the Breast Cancer Association Consortium, see attachment), and use that information to inform the development of BoB CAT authorship rules.

Manuscript Writers: the small group of people who, even if not in one of the other groups above, were crucial for bringing the manuscript to its final form through detailed critical review and substantial comments (or extensive rewriting), which led to substantial revision of the draft manuscript. See Authorship Appendix for details.

**Manuscript minimum expectations for participation and authorship**

We expect all authors as a minimum to have voted in all three rounds of the statements and to have taken an active role in BOB CAT preferably authoring one or more statements and/or contributing to the governance processes or other matters relating to the progress of the research.

Two reminders to vote will be sent and thereafter individuals will be excluded from the process.

**Leadership Team (The Core Group)**

Includes those who provided substantial time and effort into the creation and ongoing efforts of the project, in the event some people are not in one of the next two groups.

a) The executive group resides within the CORE group and comprises Janusz Jankowski, Cathy Bennett, Mark Ferguson, Paul Moayyedi, Nimish Vakil, John Inadomi.
b) Topic Area Leaders: includes people who created many of the original questions, reviewed large areas of literature, coordinated other authors around that topic area, and who wrote the summaries that formed the body of much of the manuscript (i.e. the manuscript writers).

**Ethical Issues and complaints that arise during the process**

These will be handled by an external committee – AGA ethics (J Inadomi and N Vakil will act as liaison to be confirmed).

**Conflict of Interest**

To ensure transparency and declaration of any potential bias, we require all BoB CAT members to declare any competing financial and non-financial interests when they join BoB CAT and when new interests arise i.e. those which arise at all stages of the process and not limited to authors and those involved in manuscript production (we will adopt the ICMJE Form for Disclosure of Potential Conflicts of Interest form, http://www.icmje.org/coi_disclosure.pdf).

We will additionally request an update at major milestones in BOB CAT (for example voting rounds), in the first of the year and prior to each publication.

Competing financial interests are defined as being perceived as potentially influencing the content, objectivity of behavior or integrity in discussing the group's activities.

These include but are not exclusive to the following:

- Funding: Research support (including salaries, equipment, supplies, reimbursement for attending symposia, and other expenses) by organizations that may gain or lose financially through this publication.
- Employment: Recent (while engaged in the research project), present or anticipated employment by any organization that may gain or lose financially through this publication.
- Personal financial interests: Stocks or shares in companies that may gain or lose financially through publication; consultation fees or other forms of remuneration from organizations that may gain or lose financially; patents or patent applications whose value may be affected by publication.
- Allegiance with campaigns and pressure groups should be declared.
- Consider carefully any competing financial interests that could embarrass you following publication.
- Non-financial interests include but are not exclusive to the following;
- Citing your own work at the expense of more pertinent work of others, excluding the relevant work of competitors, cronyism and nepotism. In addition complaints should be made either directly to the senior author or directly to the AGA ethics committee.
- The majority of Conflicting Interests will relate to a particular issue and as such will not present any long term restrictions on an individual's ability to work in BOB CAT. Participants should declare COI at the start of the process as well as at publication stage.

- COI declarations will be returned to the Convenor (JJ) and any other details supplied by participants stored securely at his host institution (for reasons of data protection). COI declarations will be reviewed by the Convenor and core group. In the case of any serious COI or complaint being made, the Convenor will make informal investigations to obtain further information (reference pages 9-10 of attached research conduct code Informal investigations) and then if serious evidence exists, pass the original complaint to the AGA Ethics Committee for further (more formal) investigation and action.

- BOB CAT participants are also bound by COI and research conduct codes of their host institution in additional to our local and any AGA procedures.

- If COI issues arise (potential COI violations and in the case of accusations) we will refer them to the American Gastroenterological Association committee on ethics for deliberation. We will also seek advice from the AGA to resolve proven COI. The options for resolution may include full declaration, stepping down from that statement, not voting in those statements, or stepping down from BOB CAT altogether etc.

- If any serious complaint is upheld, BOB CAT participants must comply with a direction made by the Convenor of BOB Cat and of the AGA ethics committee in relation to a conflict of interest in research.

**6. Key questions to be addressed**

PICO Overview for BoB CAT

1. Population. Unless otherwise stated the population will include patients with non-dysplastic Barrett's metaplasia. Papers should be grouped into those using IM (North America) and those using any form of metaplasia (Europe, Australasia).

Separate searches and questions formulation should be repeated for Barrett's metaplasia with either indefinite or LGD. Once again papers should be grouped into those using IM (North America) and those using any form of metaplasia (Europe, Australasia).

2. Intervention. For the various topics this will be different; Pathology (routine pathology, special stains, expertise of pathologist, number of pathologists, pathology processing, pathology reporting); Routine Endoscopy (setting agreed endoscopic landmarks, setting landmarks for irregular exophytic lesions, setting criteria for recognition of Barrett's, setting criteria for endoscopic biopsy regimen); Epidemiology (demographic features allowing stratification of risk BMI, hip/waist ratio, age, gender, ethnicity, severity of symptoms, duration of symptoms, BM length, BM stricture, smoking, family history, alcohol consumption, indefinite for dysplasia, LGD); Translational science and Molecular Pathology (best biomarkers for stratification including p53, aneuploidy, tetraploidy, p16 LOH/methylation, inherited genetics, others); Cost economic modeling (surveillance alone 'watch and wait', EMR, EMR and ablation, surgical fundoplication); Advanced Imaging (Zoom, Confocal, NFI, etc.), Therapeutic Endoscopy (EMR alone, EMR and RFA Ablation, argon, length of training, numbers of procedures per year); Medications (PPI therapy, type, duration of treatment and dose, Aspirin therapy length and dose); Patient Issues; (is complete ablation success?, is low or no cancer risk success, is not having to come back for surveillance success); Surgery (Nissen, ESD).

3. Comparator. Since most studies will be case series or cohort studies comparator groups will often be very poorly quantified. E.g. surveillance vs. no surveillance may cause us problems and we will have to properly identify comparators. Try to define this as the group not getting the intervention above

4. Outcome. Outcomes such as prevention of cancer (5 year cancer free survival), prevention of HGD, or even a surrogate, such as ablation of Barrett's.

Questions to be discussed at The International Society for Diseases of the Esophagus meeting (ISDE) in Italy on October 2012. The questions are grouped by areas of expertise.

**BOB CAT QUESTIONS**

**See Appendix BOB CAT Tracker Table, for all BOB Cat statements.**

**7. Membership of group:**

**Core Group** (20 people and chair of panel): There will be a core writing group to agree on the format of the meeting (see appendix 2 table)

This group will be co-ordinated by Cathy Bennett (formerly Cochrane Collaboration) and will take part in telecons, emails and face to face meetings.

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**Working and Consensus Panel:** (20+ countries and 150+ experts (gastroenterologists, GI surgeons, nurse specialists, patients and GI pathologists)). This panel will be sent all documents to comment upon. Membership will be open to any specialist and will be advertised in GI journals including GUT (see appendix 2 table).

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**8. Funds**

**Funding needed:**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Costings for Bob CAT in USD ($) | | | | | | | |
| Draft 7th March | | | | | | | |
| | | | | | | | |
| **Item** | **Timescales (months)** | | | | | | |
| | 1 to 3 | 3 to 6 | 6 to 9 | 9 to 12 | Completion and authoring | | TOTAL |
| **Searches*** | 6000 | | | | 1000 | | 7000 |
| **Web Based Evidence Application (Stuart Gittens EDC solutions)** | 2500 | 2250 | 2250 | 2250 | 2250 | | 11500 |
| **Consultancy fees (CB, Systematic Research Ltd, UP TO 0.5 day per week, based on £250 per day)** | 2000 | 1600 | 1600 | 1600 | 1600 | | 8400 |
| **Admin support person (Admin person 1.0 day per week), based on £125 per day** | 2500 | 2400 | 2400 | 2400 | 2400 | | 12100 |
| **Consumables and telecon fees** | 500 | 500 | 500 | 500 | 500 | | 2500 |
| **Conference meetings, room bookings etc.** | | 3000 | | 1000 | | | 4000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Travel to meetings** | | 4500 | | | | | 4500 |
| **GRAND TOTAL** | | | | | | | **50000** |
| | | | | | | | |
| *** Based on a Cochrane type search costing £4000 or smaller more focussed searches for each of the nine topic areas costing more in total.** | | | | | | | |

**9. Timescale**

**Timing and key dates**

1. Project set up

ISDE endorsement and small funding secured March 2012

Initial format finalized by May 2012

ACG and AGA endorsement and funding sought June 2012

2. Project commences and telephone consensus

Submitting questions, PICO breakdown, inviting participants.

Questions agreed by end July 2012

Upload for initial vote beginning Aug 2012

Initial voting round on basis of clinical relevance to 'shortlist' of questions for full statement development. (Search strategies in progress)

Statement development August/September 2012 (literature selections in progress)

Retrieval of declarations conflicts of interest Oct 2012 at ISDE 2012

Key leads prepare evidence based data Oct 2012

Questions with first round ‘electronic’ voting January 2013

Questions with second round answers for ‘electronic’ voting by all members Feb 2013

Review of votes and consensus March 2013

Presentation at BSG Liverpool UK March 2013

Questions with revised answers for final ‘electronic’ voting by all members May 2013

Review of final votes and consensus end May 2013

3. Project Presentations

AGA San Diego USA may 2012

DDF/BSG, Monday 18th June from 4.30 to 5.30, Liverpool, UK

ISDE Tuesday 16th October 2012 Venice, Italy, http://www.isde2012.org/

3. Voting rounds. All to be confirmed. The BOB CAT group intends to produce a list of up to 200 statements which we will reduce to around 70. The first round of question selection (based on availability of evidence and clinical relevance) took place in October 2012, before the ISDE meeting. Voting in each round ensures continued membership).

Round 1 voting results: http://mdpub.org/bobcat

**APPENDIX 1**

We will send questionnaires to the CORE group to gain information to guide the search for evidence. We will ask for which key words should be incorporated into the search strategy (to be designed and run by information science experts), for opinions on the level of evidence to be sought, the languages and databases, types of medical evidence system to grade the studies retrieved by the literature search and for any additional contributors to the working group.

The potential results are shown in Table 1 and the suggested key words are in Table 2.

**Table 1**

**Summary of questionnaire responses**

| ITEM | RECOMMENDATION |
|---|---|
| **KEY WORDS** | **Incorporate key words into search strategy to be designed by experts. (Incorporate search terms from NICE, who are running a more focused review on endotherapy for HGD)**<br><br>**See Table 2** |
| **TYPES OF EVIDENCE** | **Search for systematic reviews, meta-analyses, RCTs, non-randomised intervention studies and observational studies.**<br><br>**CORE group to decide on inclusion of expert opinion in the search strategy** |
| **LANGUAGES** | **Search with no language restriction.** |
| **DATABASES:**<br><br>Cochrane UGPD Group Trials Register in CENTRAL, MEDLINE, EMBASE | **Search in all databases listed here. (CORE group to decide on inclusion of LILACS).** |

| | |
|---|---|
| ISI Web of Science<br><br>EBMR (Evidence based medicine reviews), Controlled Trials mRCT and ISRCTN<br><br>LILACS (Latin American and Caribbean Health Sciences Literature) | |
| **MEDICAL EVIDENCE SYSTEMS** | **Use GRADE medical evidence system.** |
| **OTHER CONTRIBUTORS** | **Invite potential contributors at discretion of Convenor.** |
| | |

Other factors relating to searches

Searches to be commissioned in partnership with an external information services provider. Searches to be delivered in the following format: Unique Id, Abstract, Reference, Year, Authors, Title, Journal, pdf*, category**, sub-category

**Table 2**

**Key words**

**We will conduct detailed searches for all topics using keywords.**

| Subject | Keywords |
|---|---|
| **Definition** | Barrett's, columnar, epithelium, intestinal metaplasia<br><br>Esophagectomy, Barrett's ablation, Low grade dysplasia, indefinite for dysplasia, Columnar metaplasia, CELLO, CLO, Intramucosal cancer, Histology, Pathology, Goblet Cells, neoplasia, Dysplasia |
| **Demographics, risk factors for development of HGD.** | Age, sex, gender, length of Barrett's esophagus<br><br>Use of proton pump inhibitors,<br><br>Obesity, BMI, body mass index, previous surgery<br><br>Alcohol use, tobacco use, obesity, GERD, Caucasian,<br><br>Obesity, smoking, Use of non steroidal drugs. Aspirin. Proton Pump Inhibitor Therapy. Family history of cancer. Bile acid reflux. Acid reflux. Hiatus Hernia, Prague C and M, Biopsy forceps, Race / Ethnicity |
| **Diagnosis, method of obtaining biopsies.** | Biopsy protocol, quadrant, sampling<br><br>Seattle protocol, autofluorescence, narrow band imaging, magnification endoscopy, spectroscopy elastic scattering spectroscopy, fluorescence spectroscopy, Raman spectroscopy. Optical biopsy, Protocol algorithm,<br><br>Endoscopic mucosal resection, Biopsy Protocol. Seattle Protocol. Random Biopsies. Targeted Biopsies |

| | |
|---|---|
| **Pathology (including pathological grading systems), accuracy of identification.** | Vienna classification, precancer, neoplasia, dysplasia, high grade, Intramucosal cancer, submucosal cancer, TMN classification, inflammation, Goblet Cells. Chronic Inflammation. Mucosal Inflammation' Intramucosal cancer, carcinoma in situ |
| **Progression to cancer, biomarkers, prognosis.** | Invasive, indefinite, focal, extensive, ulcer, multifocal, raised, Flow cytometry, molecular markers<br><br>Nodular, Biomarker, flow cytometry, Mucosal involvement. Carcinoma in situ. High grade dysplasia. Biomarkers such as P53, Beta catenin nuclear localization, Paris Classification, Nodular mass |
| **Staging tests.** | Endosonography, EUS, endoluminal, confocal, trimodal, magnification, Narrow band imaging, Endoscopic mucosal resection, Endoscopic mucosal resection, chromoendoscopy, CT Scanning, EMR, Mucosal resection, NBI, narrow band imaging, FICE |
| **Treatment planning including timing of treatment, endoscopy, surveillance.** | Surveillance programs, morbidity, mortality, repeat screening endoscopy, Ablation, Seattle protocol, protocol biopsy, jumbo biopsy, optical diagnosis and biopsy, Endoscopic therapy, Omit screening |
| **Medical therapies f (drug names, types of therapy)** | Proton pump inhibitors, H-2 receptor antagonists, prokinetic agents, Aspirin, non steroidal anti-inflammatory agents, COX2 inhibitiors, Non-steroidal anti-inflammatory drugs (NSAIDs), Non steroidals. Cox2 inhibitors. Aspirin |
| **Endoscopic therapies** | Argon plasma coagulation, cryotherapy, laser therapy, multi-polar electro-coagulation, radiofrequency ablation, ultrasonic therapy, light, catheter ablation, argon plasma, sclerotherapy, electrocoagulation, multipolar, heater, probe, argon, YAG, photodynamic, PDT, 5-aminolevulinic acid, circumferential, focal Barrx, Thermal ablation, ultrasonic ablation, Barrx, endotherapy<br><br>Barrx. Endoscopic mucosal resection. EMR, mucosal resection, Radiofrequency ablation (Halo technique) |

| | |
|---|---|
| **Surgical therapies.** | Ivor Lewis, Tanner, Santy, Orringer, Merendino, transhiatal, fundoplication, anti-reflux surgery, Nissen,<br><br>Da Vinci Robot esophagectomy, Laparoscopic fundoplication, Minimally invasive esophagectomy, esophageal stripping, esophageal reconstruction, hybrid esophagectomy, Dor fundoplication, partial fundoplication, total fundoplication, Toupet fundoplication, Hill Gastropexy, Hill procedure, Hill fundoplication |
| **Other keywords** | Overall survival. Quality of Life, Barrett's (O)esophagus, esophageal adenocarcinoma<br><br>All literature that discusses excluding narrative reviews. Search terms used in the NICE (UK) guideline 'Barrett's esophagus: ablative therapy for the treatment of Barrett's esophagus'. |

**Key References**

Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process
Cathy Bennett, Nimish Vakil, Jacques Bergman, Rebecca Harrison, Robert Odze, Michael Vieth, Scott Sanders, Laura Gay, Oliver Pech, Gaius Longcroft–Wheaton, Yvonne Romero, John Inadomi, Jan Tack, Douglas A. Corley, Hendrik Manner, Susi Green, David Al Dulaimi, Haythem Ali, Bill Allum, Mark Anderson, Howard Curtis, Gary Falk, M. Brian Fennerty, Grant Fullarton, Kausilia Krishnadath, Stephen J. Meltzer, David Armstrong, Robert Ganz, Gianpaolo Cengia, James J. Going, John Goldblum, Charles Gordon, Heike Grabsch, Chris Haigh, Michio Hongo, David Johnston, Ricky Forbes–Young, Elaine Kay, Philip Kaye, Toni Lerut, Laurence B. Lovat, Lars Lundell, Philip Mairs, Tadakuza Shimoda, Stuart Spechler, Stephen Sontag, Peter Malfertheiner, Iain Murray, Manoj Nanji, David Poller, Krish Ragunath, Jaroslaw Regula, Renzo Cestari, Neil Shepherd, Rajvinder Singh, Hubert J. Stein, Nicholas J. Talley, Jean–Paul Galmiche, Tony C.K. Tham, Peter Watson, Lisa Yerian, Massimo Rugge, Thomas W. Rice, John Hart, Stuart Gittens, David Hewin, Juergen Hochberger, Peter Kahrilas, Sean Preston, Richard Sampliner, Prateek Sharma, Robert Stuart, Kenneth Wang, Irving Waxman, Chris Abley, Duncan Loft, Ian Penman, Nicholas J. Shaheen, Amitabh Chak, Gareth Davies, Lorna Dunn, Yngve Falck–Ytter, John Decaestecker, Pradeep Bhandari, Christian Ell, S. Michael Griffin, Stephen Attwood, Hugh Barr, John Allen, Mark K. Ferguson, Paul Moayyedi, Janusz A.Z. Jankowski

Gastroenterology 1 August 2012 (volume 143 issue 2 Pages 336-346 DOI: 10.1053/j.gastro.2012.04.032)

**BAD CAT is accredited by NICE (UK).** The guidance has been developed to a quality process and reassures them that it will help them deliver the highest standards of patient care.

*BAD CAT consensus statement Gastroenterology journal*
*http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508512006142.pdf*
*BAD CAT accredited by NICE*
*http://www.evidence.nhs.uk/accreditation/accreditation-decisions/p-accreditation-submissions-bad-cat-accreditation-reports-final-final-accreditation-decision-report-bad-cat-1.5.pdf*

Poste G. Bring on the biomarkers. Nature. 2011 Jan 13;469(7329):156-7.

**APPENDIX 3: AUTHORSHIP GUIDELINES**

**Governance**
**Manuscript, Authorship, and Publication Guidelines**
**Adopted after majority vote by ISDE executive and BOB CAT Core group, November 2012**

Introduction

We recently asked the ISDE executive committee render judgment on our process involving determining authorship criteria for the BOBCAT consensus process. The challenge is that getting agreement of authorship in such a prestigious undertaking cannot be left only to one or two individuals. ISDE's involvement is based on the fact that the ISDE is the largest stakeholder in this process (first and largest financial contributor to the process; ISDE originated the concept of these consensus processes for Barrett's) and that the ISDE executive committee is viewed as a streamlined group that can render such decisions efficiently.

Mark Ferguson and Janusz on the group's behalf asked ISDE executive committee vote yes or no in support of the following process for selecting authors for the initial manuscript that comes out of the BOBCAT consensus activity

**The ISDE executive supported the publication strategy (majority 7 out of 10 votes in favour) in November 2012. BOB CAT core group voted in favour by 14 out of 21 votes in favour. BOB CAT will now adopt the publication strategy.**

Authorship Committee: Doug Corley, Yvonne Romero, Giovanni Zaninotto, Peter Watson.

**1.0 Introduction**

The purpose of BOBCAT is to produce at least one, and possibly multiple, collaborative analyses and manuscripts. The purpose of this section is to outline the goals and processes for determining the creation and authorship of these manuscripts.

**The main goals of the BOBCAT publication guidelines, which will guide decisions, are, in order of priority, to:**

- Create a high quality manuscript which meet criteria for quality and authorship
- Publish the manuscript in the highest quality journal feasible, to maximize impact
- Maximize inclusion of authors who participated to recognize efforts, for persons who meet authorship criteria
- Ensure equitable distribution of authorship within and across sites

Additional goals of the guidelines are to:

- Ensure that the content of manuscripts, if more than one is produced, do not significantly overlap and that similar or compatible approaches are used across manuscripts
- Ensure that authors meet authorship criteria
- Provide a standardized and rigorous internal review to ensure that published research meets standards for quality
- Create mechanisms for resolving disparate viewpoints regarding manuscript preparation or authorship

### 1.1 Manuscript Proposal

A Manuscript Proposal Request should be submitted to the BOBCAT steering committee. The Request should include: working title of manuscript; name of lead member, names and affiliations of any individuals who have already expressed interest in participation; hypotheses to be tested; data to be used; criteria for authorship (any specific expectations beyond those outlined below) and expected timeline.

The Steering Committee will review the proposal to discuss overlap with other manuscripts or conflicts with activities. If no issues are raised during the review, the proposal is approved. Otherwise, the proposal will be assigned to one of two categories: revise and resubmit, or disapproval.

### 1.2 Writing Group Formation

Once a Manuscript Proposal has been approved by the Steering Committee, interest in participating in activities associated should be solicited through one or more of:

- The manuscript lead alerts BOBCAT members using the BOBCAT electronic mailing list.
- The Steering Committee co-chairs alert BOBCAT members in the same manner.
- Manuscript project opportunities are announced at the BOBCAT scientific meetings.
- Additional members can be added to the writing group throughout the project as needed.

The writing group leader sends the final writing group membership list to the Steering Committee for approval.

### 1.3 Manuscript Development

6.1.3.1 Writing Group Leader

The writing group leader has overall responsibility for manuscript development, submission, communication with the journal, and revision for publication.

Rights:

- Unless otherwise determined in advance, the writing group lead will be designated as first author.

Specific responsibilities:

- Manage writing group communications.
- Create a draft outline of initial manuscript and distribute to co-authors.
- Coordinate the writing of each section of the manuscript.
- Coordinate final integration and editing of all sections and approval by all authors.
- Determine, in consultation with co-authors and the Steering Committee, potential journals for submission.
- Create, in consultation with co-authors, the Authorship Committee group, and the Steering Committee, authorship and authorship order based on the relative contributions of each author and generally-accepted practices of publication. Although the writing group leader will generally be the first author, this is not required and the leader may be delegate it to another person, at their discretion.
- Submit the final draft of the manuscript to the Steering Committee for review.
- Submit the approved manuscript for publication and coordinate the response to reviewers.
- Provide progress updates to the Steering Committee at key milestones—when the manuscript is submitted, when it is returned for revision, when it is resubmitted, when it is accepted, when it is published—and whenever requested by the Steering Committee.
- Ensure that BOBCAT funding support is listed in the manuscript

### 1.4 Writing Group Members

The Writing Group will consist of 4-6 members who actively participate in all aspects of the writing process. Its composition will be determined by the Steering Committee. Specific responsibilities include the following, although not all writing group members will have all responsibilities:

- Participate in development of the manuscript outline.
- Complete writing assignments per the requested timeline.
- Organize and analyze data to complete the assignments, as appropriate.
- Participate in discussions to determine potential journals for submission.
- Respond to requests for review and editing of manuscript drafts within specified timelines.
- Respond to recommended revisions from peer review within specified timelines.
- Accept responsibility for the accuracy and content of the final manuscript in its entirety.

**Writing Group members:**

The writing team comprises:

- ***Head of writing team (PM)***
- ***Abstract JI (lead) PM, CB, JI, NV, MF, SS, DC***
- ***Introduction JJ (lead)***

- ***Methods and data CB (lead) (+GZ, GG, DC as contributors)***
- ***Results PM (lead) (+ JJ, CB, JI, NV, DC, MF, SS, as contributors)***
- ***Discussion NV (lead) (+ JJ as contributor)***
- ***References DC (lead)/PM***
- ***Figures YR/MF/SS/PW lead (constructs data summaries, and drafts figures) with advice from PM***

The above-cited individuals will comprise the first 5-6 and the last 5-6 authors on the manuscript, provided that they meet the criteria for authorship (Section 1.7).

### 1.5 Authorship Criteria Outside of Writing Group Members

- Authorship will be determined by the Writing Group in consultation with the Authorship Committee in accordance with these guidelines.
- The final authorship will be approved by the Authorship Committee. The Authorship Committee will consist of 3-4 members appointed by the Steering Committee. Approval of authorship contents and order will require the unanimous consent of all members.

### 1.6 Authorship Dispute Resolution

If consensus cannot be reached by the Authorship Committee, or if there are disagreements from potential authors or members of the Writing Group regarding the authorship inclusion or authorship order that is approved by the Authorship Committee, a final decision will be determined by a two thirds vote of the Steering Committee.

Authorship guidelines from the International Committee of Medical Journal Editors are to be used as the framework for determining authorship (see http://www.icmje.org/). Members of the Steering Committee or Authorship Committee who are not members of the Writing group and/or who do not participate in at least one of the tasks outlined below will not be considered authors but may be considered for acknowledgement. In accordance with the ICMJE guidelines, authorship on BOBCAT manuscripts must at a minimum meet these three criteria:

1) Substantial contributions to conception and design (if possible we will request that members of the Core group can be acknowledged in the publication), acquisition of data, or analysis and interpretation of data;

2) Drafting the article or revising it critically for important intellectual content; and

3) Final approval of the version to be published.

**Authors who are not part of the writing group will be considered as authors only if they completely fulfil at least one of the following:**

- Complete required tasks as a Section Lead within timelines for the acquisition of articles, summary of data, and writing of summaries for specific questions
- Demonstrate active participation in the scientific review of articles and the review process, by completing at least 80% of voting rounds (voting rounds that concern evidence-based statements)
- Substantively assist writing group members in the development of the manuscript outline, data analysis, data interpretation, or manuscript preparation.

**Authors who are not part of the writing group must also complete the following tasks:**

- Provide critical review and approval of the version to be published with reasonable deadlines (at least 2 weeks)
- Provide signatures or approvals within reasonable publication deadlines (at least 2 weeks)

### 1.7 Authorship and Author order

Authors and authorship order should be tentatively and conditionally established once the writing group is formed, assuming that tasks will be completed. The final determination of authors and authorship, after proposal by the Writing Committee, will be finalized as described above.

- There is no limit on the number of authors for BOBCAT purposes (and that these names should be searchable in PubMed).
- If the target journal limits the number of authors a corporate authorship of “The BOBCAT Research Team” the following strategy will be employed:
  the names of the lead author, writing team and then the ‘BOB CAT consortia’ appear in the main BOB CAT paper, with names searchable in PubMed followed by the corporate authorship of "The BOBCAT Research Team". The names of the full corporate group will be listed at the end of the paper.
- Order of authors: (PM, CB, JI, SS, YR, GG/Y F-Y, GZ ..... PW, DC, NV, MF, JJ,) first author PM and then CB (joint first), then JI, SS, YR
- Last author JJ and then MF, NV, DC and PW
- The first five to six and last five to six authors will be expected to undertake all roles including writing, statement support, meeting the minimum voting criteria for the rounds and meeting the criteria for reviewing and providing feedback on a manuscript in a timely fashion, and that if unable to fulfil this role, his or her place will be taken by other authors who will be credited accordingly in the citation list.

### 1.8 Acknowledgements

Each manuscript should acknowledge persons who contributed substantially to the project described in the manuscript but who are not part of the writing group AND who don’t otherwise satisfy the International Committee of Medical Journal Editors criteria for authorship (see below). Persons included in this section are at the discretion of the Writing Group and Steering Committee and may be listed as members of an individual center or as part of the BOBCAT group. Persons listed in acknowledgement sections will be listed by the United States National Library of Medicine and therefore must approve of their acknowledgement by signing any release forms by the required deadlines.

### 1.9 Manuscript Review

Once the writing team has a manuscript that they believe is ready to be submitted to the journal of interest, following review and approval by all listed authors, the lead should submit the manuscript to the Steering Committee.

The Steering Committee (or assigned members) reviews the paper for scientific content as well as adherence to administrative requirements. The Steering Committee reviewers will check for the following:

- Each participating BOBCAT Center name and funding number appears according to the preference of the BOBCAT Center Principal Investigator.
- The affiliation of the manuscript with BOBCAT is clearly acknowledged and adequately described.
- There are no conflicts between the publication and ongoing BOBCAT projects.

- There are no conflicts with other BOBCAT papers or writing groups.
- There are no serious or major scientific flaws in study design or data interpretation.
- The findings in the manuscript are interpreted in light of the broader BOBCAT knowledge base; e.g., if findings are different from those of other BOBCAT studies, the differences are examined and explained where possible.
- All required regulatory agency approvals are appropriately acknowledged.

The Steering Committee reviews manuscripts within two weeks of receipt. Members submit comments to the Steering Committee, who will then compile the comments and forward to corresponding author, who may or may not be the working group lead.

The corresponding author decides about the incorporation of Steering Committee feedback into the manuscript. If the corresponding author does not agree with a particular major comment, he or should contact the Steering Committee co-chairs, who will then advise on next steps.

If there are no comments from the Steering Committee within the two-week review period, journal submission may proceed.

END.