Diagnosis, staging and treatment of patients with gestational trophoblastic disease
National Clinical Guideline No. 13

November 2015
Guideline Development Group
The National Clinical Guideline on the diagnosis, staging and treatment of patients with gestational trophoblastic disease (GTD) in Ireland was developed by the National Cancer Control Programme (NCCP), in collaboration with clinicians, librarians and stakeholder groups.

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Notice to Health Professionals and Disclaimer
The Guideline Development Group’s expectation is that health professionals will use clinical knowledge and judgement in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgement in such a decision must be clearly documented. Care options should be discussed with the patient, her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary.
National Clinical Effectiveness Committee

The National Clinical Effectiveness Committee (NCEC) was established as part of the Patient Safety First Initiative. The NCEC is a partnership between key stakeholders in patient safety. NCEC’s mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

**NCEC Terms of Reference**

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
9. Establish sub-committees for NCEC workstreams.

Using this National Cancer Control Programme National Clinical Guideline

The NCCP is part of the Health Service Executive (HSE) and was established in 2007 to implement the recommendations of the National Cancer Strategy. The NCCP is responsible for national cancer control by helping to prevent cancer, treat cancer and increase survival and quality of life for those who develop cancer, by converting the knowledge gained through research and surveillance into strategies and actions. The need to follow evidence-based clinical guidelines covering a patient’s journey from early detection, diagnosis, treatment, monitoring and end-of-life care is a key priority for the NCCP.

It is critical to have a range of health professionals working together to plan and deliver care for cancer patients. The target users of the guideline are the multidisciplinary clinical team caring for patients with gestational trophoblastic disease.

The development of this National Clinical Guideline would not have been possible without the enormous contribution of the members of the Guideline Development Group, the NCCP Guideline Steering Group and the reviewers. We are grateful for the commitment shown by all who contributed to the development of this guideline. In particular the invaluable input of the clinicians and the HSE/hospital librarians in this process is acknowledged and we thank them for giving generously of their time and expertise.

This National Clinical Guideline is available at: www.health.gov.ie/patient-safety/ncec and www.hse.ie/cancer

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Background

Gestational trophoblastic disease (GTD) is a spectrum of diseases that can occur during or after pregnancy, each having a varying propensity for local invasion and metastasis. GTD has been defined as a continuum of a neoplastic process that arises from the trophoblastic cells that during pregnancy are involved in the development of the placenta. Its pathogenesis is unique as it arises from gestational rather than maternal tissue (Goldstein et al., 2014). The World Health Organisation (WHO) has classified GTD as two premalignant diseases, consisting of complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), and as four malignant disorders, consisting of invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The last four conditions are often collectively referred to as gestational trophoblastic neoplasia (GTN) (Kumar & Kumar, 2011).

GTD is the most curable of all gynaecologic malignancies. It represents an oncologic success story attributable primarily to early disease recognition, chemotherapy regimens, and accurate and reliable assessment of disease status with sensitive assays for the measurement of human chorionic gonadotropin (hCG) levels. Its importance as a disease status cannot be overstated to the general gynaecologist, who is initially responsible for the diagnosis and management of GTD as well as the timely referral of the patient to a gynaecological oncologist. The management of these women is specialised and, in many countries, is undertaken by gynaecological and medical oncologists with special expertise in treating this disease. A structured approach to diagnosis and management will result in a cure for most patients, even in the setting of advanced disease, without adversely affecting future fertility (McGee & Covens, 2012).

The outcome for more than 98% of women with GTN is excellent however a small number of women will die from the disease, mainly due to late presentation and diagnosis or drug resistance (Seckl et al., 2010). According to figures from the Hospital In-Patient Enquiry (HIPE) database, in Ireland, on average, 105 new cases of GTD were diagnosed annually between the period 2005 to 2013. This guideline aims to improve the standard of clinical practice to ensure that young women affected by GTD are diagnosed promptly and receive the best available care. Further information on the epidemiology of GTD is available in Appendix 1.
There are eight hospitals designated as cancer surgery centres and one satellite breast unit (Letterkenny General Hospital). As well as these designated cancer centres, other hospitals provide cancer services such as chemotherapy (Figure 1).

There are 19 maternity units throughout the country:

**Table 1: Maternity Services in Ireland**

<table>
<thead>
<tr>
<th>Region</th>
<th>Maternity Units</th>
</tr>
</thead>
</table>
| **Dublin**        | Coombe Women’s Hospital  
                   | National Maternity Hospital, Holles Street  
                   | Rotunda Hospital |
| **South & South-East** | Cork University Maternity Hospital  
                   | Kerry General Hospital, Tralee  
                   | South Tipperary General Hospital  
                   | St Luke’s General Hospital, Kilkenny  
                   | Waterford Regional Hospital  
                   | Wexford General Hospital |
| **West & North-West** | Galway University Hospitals  
                   | Letterkenny General Hospital  
                   | Mayo General Hospital, Castlebar  
                   | Portiuncula Hospital, Ballinasloe  
                   | Sligo General Hospital |
| **Mid-West**      | University Maternity Hospital, Limerick |
| **North-East**    | Cavan/Monaghan Hospital Group  
                   | Our Lady Of Lourdes Hospital, Drogheda |
| **Midlands**      | Midlands Regional Hospital Mullingar  
                   | Midlands Regional Hospital Portlaoise |
1.1 The rationale for a National Clinical Guideline

In 2006, the second national cancer strategy, A Strategy for Cancer Control in Ireland (DoHC, 2006), advocated a comprehensive cancer control programme. It was recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care.

The principal objective of developing these guidelines is to improve the quality of care received by patients. Other objectives include:
- Improvements in the quality of clinical decisions,
- Improvement in patient outcomes,
- Potential for reduction in morbidity and mortality and improvement in quality of life,
- Promotion of interventions of proven benefit and discouragement of ineffective ones, and
- Improvements in the consistency and standard of care.

1.2 Clinical and financial impact of GTD

The diagnosis, staging, and treatment of patients with GTD requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery and chemotherapy.

A recent population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer is estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). Across the EU, the cost of cancer healthcare was equivalent to €102 per person, but varied substantially from €33 per person in Lithuania to €171 per person in Germany.

In Ireland, inpatient care costs were estimated to account for €417 million of cancer-related healthcare costs out of a total of €619 million. Drug expenditure accounted for a further €127 million, while primary-, outpatient- and emergency-care were estimated at €32 million, €30 million and €13 million, respectively (Luengo-Fernandez et al., 2013). With cancer incidence expected to increase by 99% by 2040 (NCRI, 2014), there could be a significant increase seen in healthcare costs per person in Ireland.

We currently do not have any information on the cost of GTD related care in Ireland, however, the establishment of the National GTD Registry, Monitoring and Advisory Centre will have the potential to identify the volume of patients with GTD in the country, which should inform costs.

1.3 Objectives of the National Clinical Guideline

The overall objectives of the National Clinical Guideline No. 13 ‘Diagnosis, staging and treatment of patients with GTD’ are:
- To improve the quality of clinical care,
- To prevent variation in practice,
- To address areas of clinical care with new and emerging evidence,
- Based on the best research evidence in conjunction with clinical expertise,
- Developed using a clear evidence-based internationally used methodology.

1.4 Scope of the National Clinical Guideline, target population and target audience

1.4.1 Scope

This National Clinical Guideline was developed to improve the standard and consistency of clinical practice in line with the best and most recent scientific evidence available.
This guideline focuses on the diagnosis, staging, and treatment of patients with GTD. This guideline does not include recommendations covering every aspect of diagnosis, staging, and treatment. This guideline focuses on areas of clinical practice:

- known to be controversial or uncertain,
- where there is identifiable practice variation (2.2.3, 2.2.4, 2.3.1)
- where there is new or emerging evidence,
- where guidelines have potential to have the most impact.

This guideline focuses solely on the clinical management of patients with GTD. The NCCP in partnership with the Irish Cancer Society has commenced a cancer survivorship programme. The main goal for the NCCP Survivorship Programme is to empower patients to achieve their best possible health while living with and beyond a diagnosis of cancer. This involves providing information, guidance and support to survivors and healthcare professionals in relation to healthy lifestyle, disease prevention and control. It aims to promote a good quality of life and prolonged survival for people who experience cancer.

A National GTD Registry, Monitoring and Advisory Centre (referred to in this document as the National Registry) is currently in the process of being set up and protocols in relation to the information flow to the centre are being prepared. Patient and clinical information (website information and leaflets) and statements of information practice (which includes information on the purpose of gathering data and the safeguards that are in place to protect it and how service users can access information held about them) are being prepared.

1.4.2 Target population

Patients that are covered by this guideline are:

- Women who have had a miscarriage, any woman who has had a molar pregnancy, any woman with unexplained elevated hCG, any woman presenting with metastatic disease of uncertain origin where the hCG is elevated, and any woman with atypical placental site nodules.

1.4.3 Target audience

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with GTD, such as gynaecologists, radiologists, pathologists, surgeons, medical oncologists, GPs and nursing staff. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with GTD and their significant others.

1.5 Governance

Governance of the guideline development process was provided by a multidisciplinary Guideline Steering Group which was chaired by the Director of the NCCP. Membership included representatives from all relevant disciplines and the chairs of each NCCP Guideline.
Development Group (GDG). Details of GDG members and Guideline Steering Group members are available in Appendices 2 and 3. Figure 2 outlines the stages of guideline development.

A GDG was responsible for the development and delivery of the National Clinical Guideline and included representatives from relevant medical groups (gynaecologists, surgeons, and medical oncologists) with expertise in the diagnosis, staging and treatment of patients with GTD. The GDG also included two project managers, a methodologist and a clinical librarian.

1.5.1 Conflict of interest statement

A conflict of interest form (see NCCP Methodology Manual: Appendix II) was signed by all GDG members and reviewers. Members of the GDG declared no conflicts of interest.

The GDG was managed by the chair to promote the highest professional standard in the development of this guideline.

1.5.2 Funding body and statement of influence

The guideline was commissioned and funded by the NCCP however the guideline content was not influenced by the NCCP or any other funding body. This process was fully independent of lobbying powers. All recommendations were based on the best research evidence integrated with clinical expertise.
The Stages of Guideline Development

National Cancer Control Programme (NCCP)
NCCP Executive Team mandates the development of a National Cancer Guideline

NCCP Guideline Steering Group
Provides overall governance of guideline development

Guideline Development Group (GDG)
Is established and a Chair is appointed
Conflicts of interest must be declared by all members
Guideline development training is completed

Methodology
Step 1: Develop clinical questions
Step 2: Search for the evidence
Step 3: Appraise the literature for validity and applicability
Step 4: Formulation and grading of recommendations

Draft Guideline

National Stakeholder Review
National opinion is sought
Feedback reviewed
Draft guideline amended

International Expert Review
International expert opinion is sought
Feedback reviewed
Draft guideline amended

Pre-publication check (incl. literature update)

NCCP guideline submitted to NCEC

Implementation

Evaluation/Audit

Figure 2 The Stages of Guideline Development
1.6 Guideline methodology

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual 2014 for guideline development.

1.6.1 Step 1: Develop clinical questions

The first step in guideline development was to identify areas of new and emerging evidence or areas where there was variance in practice. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

To formulate the clinical questions they were broken down into their component parts using the PICO(T) framework:

- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time.

This process was carried out by discipline specific sub-groups. The GDG signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 16 clinical questions are listed in Appendix 4.

1.6.2 Step 2: Search for the evidence

The first step in searching for the evidence is the identification of international guidelines. Searches of the primary literature were only conducted if the answers to the clinical questions were not found in up to date evidence based guidelines.

The clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP (Appendix 5). The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:

- Cochrane Library
- Point-of-Care Reference Tools
- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. All literature searches were updated prior to publication and are current up to January 2015. A full set of literature search strategies is available on the NCCP and NCEC websites.

Details of the search strategy undertaken for the budget impact assessment are available in Appendix 11.

1.6.3 Step 3: Appraise the literature for validity and applicability

International guidelines were appraised using the international, validated tool; the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).
There were three main points considered when appraising all the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of this guideline? (external validity).

1.6.4 Step 4: Formulate and grade the recommendations

The evidence which addressed each clinical question, both from international guidelines and primary literature, was extracted into evidence tables. Recommendations were formulated through a formal structured process. A ‘considered judgment form’ (adapted from SIGN; see NCCP Methodology Manual 2014: Appendix VII) was completed for each clinical question.

The following items were considered and documented:

- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Is the evidence consistent?
  - Is the evidence generalisable to the Irish population?
  - Is the evidence applicable in the Irish context?
  - What is the potential impact on the health system?
- What is the potential benefit versus harm to the patient?
- Are there resource implications?

The evidence statements and recommendations were then written. Each recommendation was assigned a grade by the GDG. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence tables and grading systems used are documented in Appendix 6.

Good practice points were based on the clinical expertise of the GDG.

For the economic literature, key messages are presented in boxes entitled ‘relevance to guideline recommendations’.

1.7 Patient advocacy

The views and preferences of the target population were sought by inviting patient advocacy groups (HSE Patient Forum, Irish Cancer Society, Cancer Care West, Marie Keating Foundation, Gary Kelly Cancer Support Centre, Bray Cancer Support Centre, and The Miscarriage Association of Ireland) to engage in the National Stakeholder Review process (Appendix 7).

1.8 National stakeholder and international expert review

The draft guideline was signed off by the entire GDG, the wider Gynaecology Tumour Group, and the NCCP Guideline Steering Group before going to national stakeholder review. It was circulated to relevant organisations and individuals for comment between 24th June and 5th August 2014. A full list of those invited to review this guideline is available in Appendix 7.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided (NCCP Methodology Manual 2014: Appendix VIII) along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments.
All feedback received was reviewed by the project managers and research team. Suggested amendments and supporting evidence were reviewed by the guideline development group and consensus reached to accept or reject the amendments. Amendments were rejected following discussion between members and in instances where no superior evidence was provided or no conflict of interest form was provided. All modifications were documented.

The amended draft guideline was then submitted for international expert review. The GDG nominated two international experts to review the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the National Stakeholder Review. The guideline was circulated for comment between the November and December 2014.

A log was recorded of all submissions and amendments from the national stakeholder review and international expert review process.

1.9 Procedure for updating the National Clinical Guideline

This guideline was issued in November 2015 and will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be subject to the NCEC approval process and noted in the guidelines section of the NCCP and NCEC websites.

1.10 Implementation of the National Clinical Guideline

The implementation plan is based on the COM-B theory of behaviour change (Michie et al., 2011), as outlined in the NCCP Methodology Manual 2014. The implementation plan outlines facilitators and barriers to implementation (Appendix 8).

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available on the NCCP and NCEC websites.

A multidisciplinary clinical team is responsible for the implementation of the guideline recommendations. Recommendations have been divided into the key areas of diagnosis, staging, and treatment.

All priorities in relation to GTD care are agreed annually by the NCCP and are submitted to the annual HSE Service Plan, which is published on the HSE webpage. The NCCP Cancer Guidelines will be included in the annual service planning process.

1.11 Tools to assist the implementation of the National Clinical Guideline

A list of relevant tools to assist in the implementation of the National Clinical Guideline is available in Appendix 9.

1.12 Audit

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care. For audit criteria see Appendix 10.
1.13 **Budget impact**

Many recommendations in this guideline represent current standard practice and are therefore cost neutral. However, the GDG has identified the areas that require change to ensure full implementation of the guideline. The potential resource implications of applying these recommendations have been considered (appendix 11). In areas where additional resources are required these will be sought through the HSE service planning process.

1.14 **Organisational responsibility**

This National Clinical Guideline should be reviewed by the multidisciplinary clinical team and senior management in the hospital to plan the implementation of the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline.

All clinical staff with responsibility for the care of patients with GTD are expected to:

- Comply with this National Clinical Guideline and any related procedures or protocols,
- Adhere to their code of conduct and professional scope of practice as appropriate to their role and responsibilities, and
- Maintain their competency for the management and treatment of patients with GTD.

1.15 **Glossary of terms and abbreviations**

A glossary of the terms and abbreviations used throughout the guideline is available in Appendix 12.

1.16 **Accompanying documents**

The following documents are available on the NCCP and NCEC websites:

- Guideline Summary
- NCCP Methodology Manual 2014 for guideline development
- Literature search strategies.
2 National Clinical Guideline

2.1 Summary of clinical recommendations
Responsibility for implementation: The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline. Each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

There are various entry points for patients within the scope of this guideline.

2.2 Diagnosis

2.2.1 The histological assessment of material obtained from the medical or surgical management of all failed pregnancies (if available) is recommended to exclude trophoblastic disease (Grade D).

2.2.2 Ultrasound examination is helpful in making pre-evacuation diagnosis but the definitive diagnosis is made by histological examination of the products of conception (Grade C).

2.2.3 It is recommended that in all cases of suspected molar pregnancy, the preliminary pathology report should ideally be available to the clinician within 14 days (Grade D).

2.2.4 The guideline development group recommends that a National GTD Registry, Monitoring and Advisory Centre should be established for all cases of gestational trophoblastic disease (GTD) (Grade D).

2.2.5 The management of complicated cases should be discussed with the National GTD Registry, Monitoring and Advisory Centre clinical lead (Grade D).

2.2.6 For patients with complete hydatidiform mole serum human chorionic gonadotropin (hCG) is monitored weekly until normalisation for three weeks.
   • If this occurs within eight weeks then monitor monthly for six months from the time of evacuation.
   • If normalisation occurs greater than eight weeks post evacuation then monitoring continues monthly for six months post normalisation (Grade C).

2.2.7 For patients with partial hydatidiform mole the serum hCG should be monitored weekly until normalisation and one further confirmatory hCG measurement is performed 4 weeks later. If that confirmatory hCG is normal then follow up is complete (Grade D).

2.3 Staging

2.3.1 Women with gestational trophoblastic neoplasia (GTN) should have hCG, pelvic ultrasound, CT scan of abdomen & pelvis, and a chest x-ray (Grade C).

2.3.2 If metastases are present on chest x-ray a CT scan of the thorax and an MRI of the brain should be performed (Grade C).

2.3.3 Women with GTN (invasive mole, choriocarcinoma) should be assigned a FIGO score to direct management decisions of chemotherapy regimens (Grade B).

2.4 Treatment

2.4.1 Indications for chemotherapy following diagnosis of GTN:
   • Plateaued or rising hCG after evacuation,
   • Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
   • Histological evidence of choriocarcinoma,
   • Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of >2cm on chest x-ray,
   • Serum hCG of ≥20,000 IU/l more than four weeks after evacuation, because of the risk of uterine perforation,
   • Raised hCG six months after evacuation even if still falling (Grade C).

2.4.2 Patients with a FIGO score of 0-6 can be treated with either single-agent methotrexate with or without folinic acid, or actinomycin D. In most European centres, methotrexate with folinic acid is preferred because it is less toxic than methotrexate alone or single-agent actinomycin-D (Grade C).
2.4.2.2 Chemotherapy for low-risk disease should be continued for three cycles of maintenance treatment after hCG normalisation (Grade C).

2.4.3.1 Patients with a FIGO score of ≥7 should receive multi-agent chemotherapy and most centres now use EMA/CO (Etoposide, methotrexate, actinomycin D plus cyclophosphamide and vincristine), as it is highly effective, easy to administer and relatively non-toxic (Grade B).

2.4.3.2 Early deaths in ultra high-risk GTN can be reduced by induction therapy with etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EP/EMA (Etoposide and cisplatin plus etoposide, methotrexate, actinomycin D) (Grade C).

2.4.4.1 For women with low-risk GTN undergoing first-line chemotherapy, the first ± second course of chemotherapy should be administered as an in-patient at a centre with medical oncology, gynaecological services and interventional radiology (Grade C).

2.4.5.1 Monitoring during treatment low-risk: Patients should have human chorionic gonadotropin levels monitored twice a week during treatment (Grade C).

2.4.5.2 Monitoring during treatment high-risk: Patients with high-risk disease should have maintenance therapy for three cycles after hCG normalisation extended to four cycles for patients with poor prognostic features such as liver metastases with or without brain metastases (Grade B).

2.4.5.3 Follow-up post treatment: After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels (Grade C).

2.4.5.4 For women with low-risk GTN who have not responded or have relapsed from single-agent treatment (methotrexate or actinomycin D), the next line of treatment is combination chemotherapy with EMA/CO (Grade B).

2.4.9.1 Emergency Treatment - In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point (Grade C).

2.4.9.2 Hepatic metastases - In patients who are acutely unwell from liver disease emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. Patients with hepatic metastases at presentation should commence therapy using EP/EMA protocol. Given the rarity of this condition each individual case should be discussed with International experts. (Grade C).

2.4.9.3 Cerebral metastases - In patients who are acutely unwell from CNS disease emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to high dose EMA/CO at a later point using an increased methotrexate dose (1gm/m²) combined with longer FA rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the hCG normalisation. In emergency situation with cerebral metastases, high dose dexamethasone is given followed by two day EP as above. Given the rarity of this condition each individual case should be discussed with International experts. (Grade C).

2.4.9.4 Hepatic and synchronous cerebral metastases - In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. This combines the EMA (CNS) dose with the EP treatment. It misses out the day two of the normal EMA protocol as it is too myelosuppressive when combined with EP to allow for this. Given the rarity of this condition each individual case should be discussed with International experts. (Grade C).
2.2 Diagnosis

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.
Clinical question 2.2.1

Should all women undergoing medical management of miscarriage have histopathology of products of conception to exclude trophoblastic disease?

Evidence statement
The evidence for this question comes from two guidelines which state that histopathology of products of conception should be performed in all cases of surgical and medical management of miscarriage and spontaneous miscarriage (RCOG, 2010; RCOG, 2006).

Women who miscarry at home and are admitted to hospital should be advised to take with them any tissue passed so that histological examination can be arranged. The attending practitioner should arrange for the appropriate laboratory examination (RCOG, 2006).

Histopathology of products of conception enables earlier accurate diagnosis of trophoblastic disease.

<table>
<thead>
<tr>
<th>Recommendation 2.2.1.1</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>The histological assessment of material obtained from the medical or surgical management of all failed pregnancies (if available) is recommended to exclude trophoblastic disease.</td>
<td>D</td>
</tr>
</tbody>
</table>
Clinical question 2.2.2

For women with suspected molar pregnancy, what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?

Evidence statement

There is international consensus that for women with suspected molar pregnancy further tests should be done and that histopathology is the gold standard (RCOG, 2010; Mangili et al., 2014).

In the largest series of more than 1000 patients with molar pregnancy, the reported sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography were 44%, 74%, 88%, and 23%, respectively (Fowler et al., 2006; Kirk et al., 2007). (Shanbhogue et al., 2013)

Sebire and colleagues (2001) reported that ultrasonography accurately detected molar pregnancy in only 34% of 155 pathologically proven molar pregnancies. However, 84% of sonographically suspected cases of molar pregnancy were histopathologically proven (53 out of 63), indicating a high positive predictive value.

The diagnosis of hydatidiform moles is established by:
- History
- Clinical examination
- Ultrasound examination
- Serum hCG (human chorionic gonadotropin) levels
- Histopathological examination
- Cytogenetic and molecular biological examination if indicated.
  (Sasaki, 2003)

At present, genetic studies remain a useful adjunct to histopathological diagnosis in selected cases rather than routine investigation. (Sebire, 2010)

Clinicians should liaise with their local laboratory to optimise diagnosis.

<table>
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<tr>
<th>Recommendation 2.2.2.1</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Ultrasound examination is helpful in making pre-evacuation diagnosis of partial or complete molar pregnancy but the definitive diagnosis is made by histological examination of the products of conception.</td>
<td>C</td>
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</tbody>
</table>

Good practice point

GTD may be diagnosed in the absence of histopathological proof based on clinical, radiological, or biochemical suspicion (raised hCG). In these circumstances early expert referral is recommended.
Clinical question 2.2.3
For women where there is suspicion of partial or complete molar pregnancy who have an evacuation performed, in what time frame should the pathology report (post-evacuation) be available to the clinician?

Evidence statement
The evidence that informs this question comes from the fact that most women who develop persistent GTD do so within 12 weeks of evacuation (Soto-Wright et al., 1995).

Soto-Wright et al. (1995) observed that the diagnosis of complete hydatidiform mole was being made earlier in gestation, the median gestational age of complete molar pregnancy at the time of evacuation was reduced from 16 weeks (1965-1975) to 12 weeks (1988-1993). The use of ultrasound in early pregnancy has probably led to the earlier diagnosis of molar pregnancy.

Some women present acutely unwell and require chemotherapy less than two weeks post evacuation. Laboratory tests should be prioritised by histopathology departments attached to maternity hospitals in cases of suspected GTD.

<table>
<thead>
<tr>
<th>Recommendation 2.2.3.1</th>
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<tbody>
<tr>
<td>It is recommended that in all case of suspected molar pregnancy, the preliminary pathology report should ideally be available to the clinician within 14 days.</td>
<td>D</td>
</tr>
</tbody>
</table>

Good practice point
GTD may be diagnosed in the absence of histopathological proof based on clinical, radiological, or biochemical suspicion (raised hCG). In these circumstances early expert referral is recommended.
Clinical question 2.2.4

For women with gestational trophoblastic disease should management be centralised to a specialised centre(s) to ensure optimum outcome?

Evidence statement

The evidence discusses the United Kingdom model of centralisation, which has led to excellent historical outcomes and ongoing improvement. The low rate of relapse and high subsequent cure rate supports a policy of informing treated patients that they are almost certainly cured (97%), but that they should take part in a structured hCG follow-up programme because of the small (3%) chance of relapse. (Sita-Lumsden et al., 2012)

This is supported by a recent worldwide survey that demonstrated that mortality for patients with GTN primarily treated at a trophoblastic centre was 2.1% (59 of 2859 patients) compared to 8% (149 of 1854 patients) among those referred after failure of primary treatment ($P < 0.001$ by $X^2$) (Kohorn, 2014).

A centralised registry is necessary for the registration of all cases of GTD and monitoring of hCG follow-up. Care is optimised when management is centralised. The guideline development group recommends that there should be a maximum of two centres. All patients with hydatidiform mole should be registered and treated in conjunction with a specialist centre for hCG surveillance, preferably one that is coordinated nationally.

In 2013, approximately 86 patients gave rise to 195 discharges with a primary diagnosis of hydatidiform mole, malignant neoplasm of placenta or neoplasm of placenta of uncertain origin, to hospitals in the Irish public system according to data on incidences from the HIPE system.

A National GTD Registry, Monitoring and Advisory Centre for patients with GTD is currently being established in Ireland to register and audit all GTD referrals. All patients with GTD should be registered with the national GTD centre to allow centralised recording of hCG levels. The National MDT will notify the patients’ treating clinician if further intervention/treatment is needed following hCG monitoring.

**Recommendation 2.2.4.1**

The guideline development group recommends that a National GTD Registry, Monitoring and Advisory Centre should be established for all cases of GTD.

**Recommendation 2.2.4.2**

The management of complicated cases should be discussed with the National GTD Registry, Monitoring and Advisory Centre clinical lead.
Clinical question 2.2.5
For women with partial and complete molar pregnancy, what clinical and human chorionic gonadotropin monitoring protocol should be carried out to ensure they have been fully followed up and require no further therapy or monitoring?

Evidence statement
There are a number of different protocols for the follow-up of hCG levels (Charing Cross, Bagshawe et al., 1986, Alazzam et al., 2011). If hCG levels normalise within 56 days of the uterine evacuation risk of persistent subsequent disease is almost negligible. (Seckl et al., 2010)

For complete molar pregnancy serum hCG is monitored weekly until normalisation for three weeks. If this occurs within eight weeks then monitor monthly for six months post evacuation. If normalisation occurs more than eight weeks post evacuation the monitoring continues monthly for six months post normalisation (Figure 3). The current protocol is consistent with international best practice and is chosen for consistency.

![Figure 3](image-url) The current protocol for monitoring hCG levels in women with complete molar pregnancy

For partial hydatidiform mole, stopping hCG surveillance after normalisation in more than 500 patients did not result in GTN being missed. In a prospective cohort of 1,980 patients diagnosed pathologically with GTD, the risk of developing GTN (239 patients) in patients with a normalised hCG was shown to be 0.36% (4/1,122) for complete hydatidiform mole and 0% (0/593) for partial hydatidiform mole. Although these concordant data do not definitely exclude the possibility of GTN, they do suggest that the risk is too low to justify follow-up after hCG normalisation in patients with partial hydatidiform mole (Schmitt et al., 2013).

Pending further research, it may be reasonable to recommend stopping surveillance in PHM patients from the date of normalisation of hCG.

Based on suggestions from external reviewers and the guideline development group, it was agreed that patients with PHM should have their serum hCG monitored weekly until normalisation and one further confirmatory hCG measurement is performed four weeks later. If that confirmatory hCG is normal then follow up is complete.
### Recommendation 2.2.5.1

| For patients with complete hydatidiform mole serum hCG is monitored weekly until normalisation for three weeks. |
| - If this occurs within eight weeks then monitor monthly for six months from the time of evacuation. |
| - If normalisation occurs greater than eight weeks post evacuation then monitoring continues monthly for six months post normalisation. |
| Grade | C |

### Recommendation 2.2.5.2

| For patients with partial hydatidiform mole the serum hCG should be monitored weekly until normalisation and one further confirmatory hCG measurement is performed four weeks later. If that confirmatory hCG is normal then follow up is complete. |
| Grade | D |

### Good practice point

For all women with a previous diagnosis of GTD early fetal ultrasound is standard practice to ensure a normal intrauterine pregnancy and to rule out recurrence of a molar pregnancy.

### Good practice point

If a normal intrauterine pregnancy is confirmed there are no extra investigations necessary during the pregnancy and the pregnancy progresses as per any normal pregnancy.

### Good practice point

For all women with a previous diagnosis of GTD any subsequent pregnancy should be followed with a serum hCG measurement at six and ten weeks post-natally regardless of the outcome of pregnancy.

### Good practice point

Normal hCG is defined as 0-5 IU/L depending on which hCG platform is used.
2.3 Staging

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.
Clinical question 2.3.1

For women with Gestational Trophoblastic Neoplasia (GTN), what investigations should be done to accurately stage GTN?

Evidence statement

Gestational trophoblastic neoplasia (GTN) includes: invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). In the absence of tissue for a definitive histopathologic diagnosis, GTN is diagnosed as a result of persistent elevation of hCG after evacuation of a molar pregnancy. (Berkowitz et al., 2015a)

Staging investigations and treatment stratification after a molar pregnancy

Most patients developing persistent disease post-hydadiform mole (HM) are detected early via hCG monitoring and so extensive investigation is rarely required. Information to determine therapy can be obtained from the clinical history, examination, measurement of serum hCG and a Doppler pelvic ultrasound to confirm the absence of a pregnancy, to measure the uterine size/volume, spread of disease within the pelvis and its vascularity. (Seckl et al., 2013)

Ultrasound is performed to rule out pregnancy in all patients. Once pregnancy is ruled out an expert gynecological ultrasound (a specialised Doppler ultrasound of the uterus and uterine artery) or a computed tomography (CT) scan should be performed in order to accurately stage GTN. It is reasonable in the Irish context in the absence of an expert gynecological ultrasound to perform a CT scan of the abdomen and pelvis due to the transferability, reliability and reproducibility of CT scans (figure 4).

CT of the chest is not required if the chest X-ray (CXR) findings are normal, since discovery of micrometastases, which may be seen in approximately 40% of patients, does not influence outcome (Darby et al., 2009). However, if lesions are noted on CXR, magnetic resonance imaging (MRI) of the brain and CT body are indicated to exclude more widespread disease involving, for example, the brain or liver, which would significantly alter management. (Seckl et al., 2013)

All patients should have a baseline chest radiograph to evaluate for lung metastases rather than CT, since a chest radiograph, not CT, is the basis for International Federation of Gynecology and Obstetrics (FIGO) staging. (Berkowitz et al., 2015a)

Staging investigations for choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT)

Women who present with an elevated hCG and suspected GTN (CC, PSTT and ETT) following a prior pregnancy require much more extensive staging investigations, which include a contrast enhanced CT of the chest and abdomen, MRI of the brain and pelvis, a Doppler ultrasound of the pelvis and may benefit from a lumbar puncture to assess the cerebrospinal fluid to serum hCG ratio. The latter if more than 1:60 suggests occult central nervous system disease (Seckl et al., 2010). In addition, where there is doubt over the clinical diagnosis, tissue should be obtained and genetic analysis undertaken to confirm the gestational origin of the tumour through the presence of paternal genes. Some investigators have recently started using positron emission tomography/computed tomography (PET-CT) imaging, but experience is still quite limited. It appears that this imaging modality is more helpful in relapsed disease to identify sites for resection and, as with other cancers, is prone to both false-positive and false-negative results (Seckl et al., 2010). (Seckl et al., 2013)
Figure 4 Radiological investigations for patients with GTN following a HM on hCG surveillance

**Recommendation 2.3.1.1**  
Women with GTN should have hCG, pelvic ultrasound, CT scan of abdomen & pelvis, and a chest x-ray.  
**Grade C**

**Recommendation 2.3.1.2**  
If metastases are present on chest x-ray a CT scan of the thorax and an MRI of the brain should be performed.  
**Grade C**

**Good practice point**  
Investigation and management decisions should be performed by experienced professionals in this area.
**Clinical question 2.3.2**

For women with gestational trophoblastic neoplasia (GTN), what risk scoring system should be used to stage GTN?

**Evidence statement**

The International Federation of Gynecology and Obstetrics (FIGO) reports data on GTN using anatomic staging systems (Table 2) and prognostic scoring (Table 3) (FIGO, 2009).

Since 2002, all physicians treating GTN should use this system to enable the comparison of data. The prognostic score predicts the potential for developing resistance to single-drug chemotherapy with methotrexate or actinomycin D. A score of 0–6 and ≥7 indicates a low- and high-risk of resistance, respectively. The latter has almost no chance of being cured with single-drug therapy and requires multi-agent treatment. The anatomic staging not only helps with determining therapy, but provides additional information to help clinicians who compare results between centres.

**Table 2 FIGO Anatomical Staging as adapted by FIGO (2009)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Disease confined to the uterus</td>
</tr>
<tr>
<td>Stage II</td>
<td>GTN extends outside of the uterus, but is limited to the genital structures</td>
</tr>
<tr>
<td>Stage III</td>
<td>GTN extends to the lungs, with or without known genital tract involvement</td>
</tr>
<tr>
<td>Stage IV</td>
<td>All other metastatic sites</td>
</tr>
</tbody>
</table>

**Table 3 Modified WHO prognostic scoring system as adapted by FIGO (2009)**

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Pretreatment serum hCG IU/l</td>
<td>&lt;10³</td>
</tr>
<tr>
<td>Largest tumour size (including uterus)</td>
<td>&lt;3 cm</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>–</td>
</tr>
<tr>
<td>Prior failed chemotherapy</td>
<td>–</td>
</tr>
</tbody>
</table>

Staging notation uses a Roman numeral followed by an Arabic numeral that indicate FIGO anatomic staging and the WHO modified score, respectively. Placental site trophoblastic tumour (PSTT) and Epithelioid trophoblastic tumour (ETT) are classified separately (Biscaro et al., 2015). The total score for a patient is obtained by adding the individual scores for each prognostic factor: Low-risk 0-6; high-risk ≥7. Decision making based on the risk score (i.e. choosing and administering chemotherapy) should be made by experienced professionals in this area.
PSTT and ETT should not be scored and instead require separate classification in consultation with international experts (Seckl et al., 2013, Biscaro et al., 2015).

Consideration should be given to discussing borderline patients with international experts. Some reports suggest that patients with prognostic scores of 5 or 6 may be at an increased risk of resistance to single-agent chemotherapy. In a study by Taylor et al., (2013), over half the patients defined by FIGO/WHO score as low-risk (score 0–6) had a complete response to first-line treatment with methotrexate/folinic acid (60%). However, patients with a total FIGO/WHO score of 6 or hCG level of >100,000 IU/l had significantly higher rates of resistance. Only 19% of patients with a FIGO/WHO low-risk score of 6 and 16% with an hCG level of >100,000 IU/l achieved a complete response to methotrexate/folinic acid. Research is ongoing to try to better define which “low-risk” patients may particularly benefit from primary combination chemotherapy (Sita-Lumsden et al., 2012, Taylor et al., 2013).

Recommendation 2.3.2.1

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<tr>
<th>Grade</th>
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Women with GTN (invasive mole, choriocarcinoma) should be assigned a FIGO score to direct management decisions of chemotherapy regimens.

**Good practice point**

Placental site trophoblastic tumour and epithelioid trophoblastic tumour should not be scored using the FIGO system. They require separate classification in consultation with international experts.
2.4 Treatment

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.
Clinical question 2.4.1
For women with gestational trophoblastic neoplasia, what are the clinical indicators to diagnose GTN warranting chemotherapy?

Evidence statement
The United Kingdom indications for commencing chemotherapy are listed below and are broadly similar to those of the International Federation of Gynecology and Obstetrics (FIGO) (Kohorn, 2002). The commonest is a plateaued or rising human chorionic gonadotropin (hCG), but others include a tissue diagnosis of choriocarcinoma (CC) and spread to other organs. The United Kingdom (UK) experience indicates that the disease is also unlikely to spontaneously remit if the hCG is >20,000 IU/l one month after hydatidiform mole (HM) evacuation (also associated with an increased risk of uterine perforation) or there are lung or vaginal metastasis of >2 cm (smaller lesions may spontaneously regress) (Seckl et al., 2010). In addition, in the UK, chemotherapy is started to help stop heavy bleeding that requires transfusion even if the hCG is falling. (Seckl et al., 2013)

Recent data have suggested that surveillance is adequate for some women who continue to have a falling hCG six months after evacuation (Agarwal et al., 2012). However these decisions must be made on an individual patient basis following consultation with clinicians experienced in GTN management.

UK indications for chemotherapy following the diagnosis of GTN:
- Plateaued or rising hCG after evacuation*,
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
- Histological evidence of choriocarcinoma,
- Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities larger than 2 cm on chest radiograph. (Seckl et al., 2013)

- The following patients should be discussed on an individual basis with experienced professionals:
  - Women with a serum hCG of 20,000 IU/l or more, four weeks or more after evacuation, because of the risk of uterine perforation,
  - Women with a raised hCG six months after evacuation, even when hCG still decreasing.

Recommendation 2.4.1.1
Indications for chemotherapy following diagnosis of GTN:
- Plateaued or rising hCG after evacuation*,
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
- Histological evidence of choriocarcinoma,
- Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of >2 cm on chest x-ray,
- Serum hCG of ≥20,000 IU/l more than four weeks after evacuation, because of the risk of uterine perforation,
- Raised hCG six months after evacuation even if still falling.

* Plateaued or rising is defined as four or more equivalent values of hCG over at least three weeks (days 1, 7, 14, and 21) and three consecutive rises in hCG of 10% or greater over at least two weeks (days 1, 7, and 14), respectively.
Clinical question 2.4.2
For patients with low-risk (FIGO 0-6) GTN, what is the optimal first-line chemotherapy regimen?

Evidence statement
Low-risk disease is characterised by any one of the following:

- FIGO stage I GTN – This is characterised as a persistently elevated human chorionic gonadotropin (hCG) level and/or tumour confined to the uterus
- Stage II or III GTN with a WHO risk score 0-6.

For nearly all low-risk GTN patients, single-agent chemotherapy with either methotrexate or actinomycin D is the standard treatment. A variety of regimens have been developed. The variability in regimens reflects differences in dose, frequency and route of administration as well as criteria used to select patients for therapy (Berkowitz and Goldstein, 2009). Some investigators have argued that more intense therapies given daily over 5–8 days every two weeks are superior to treatments given once every two weeks (Kohorn, 2002). Others have suggested that actinomycin D is more likely to induce remission than methotrexate. The few randomised studies to address some of these issues (Osborne et al., 2011) have been underpowered and compared regimens that are not frequently used internationally (Alazzam et al., 2009). Consequently, a new larger international randomised trial has recently commenced comparing the more commonly used methotrexate regimens in Europe and many parts of the world and some centres elsewhere [methotrexate 0.4 mg/kg (maximum 25 mg) IV d1–5 every 2 weeks] (Lurain et al., 2012) with actinomycin-D (1.25 mg/m² IV every 2 weeks). Importantly, patients failing first-line therapy, usually because of resistance, can be easily salvaged with second and occasionally third-line chemotherapy so that the overall survival (OS) is ~100% (Lurain et al., 2012, McNeish et al., 2002, Sita-Lumsden et al., 2012). As survival is so high, it seems sensible to start with the least toxic therapy first to minimise the exposure of patients to more harmful treatments. (Seckl et al., 2013)

The methotrexate with folinic acid rescue regimen developed at Charing Cross hospital is effective, well tolerated and unlike actinomycin-D, does not induce hair loss, so methotrexate with folinic acid has been widely adopted (McNeish et al., 2002). (Seckl et al., 2013)

Non-randomised data suggest that reducing the consolidation therapy by just one cycle doubles the risk of relapse (Lybol et al., 2012). This provides justification for the current regimen of three consolidation cycles of methotrexate after hCG normalisation.

In a study by Hasanzadeh et al., (2014) the efficacy of weekly IM methotrexate regimen with dose escalation in low-risk GTN was 74.3%, which is the highest rate among present studies. Additionally, this study showed that the mentioned methotrexate regimen was less effective in patients with score 5 and 6, especially score 6. Therefore, more schedules should be performed to make changes in management, therapeutic protocols, and also classification of this group. Similarly in a retrospective study carried out by Taylor et al., (2013) 173/289 patients (60%) treated with methotrexate/folinic acid achieved a complete biochemical response, while 116 patients (40%) developed resistance.

Central nervous system (CNS) prophylaxis
Charing Cross hospital’s policy is to give prophylaxis to low-risk patients with lung metastases. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses. In contrast, the Sheffield unit only gives CNS therapy to those with proven CNS metastases (Charing Cross, 2015).
<table>
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<tr>
<th>Recommendation 2.4.2.1</th>
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<tbody>
<tr>
<td>Patients with a FIGO score of 0-6 can be treated with either single-agent methotrexate with or without folinic acid, or actinomycin-D. In most European centres, methotrexate with folinic acid is preferred because it is less toxic than methotrexate alone or single-agent actinomycin-D.</td>
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<tr>
<th>Recommendation 2.4.2.2</th>
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<tbody>
<tr>
<td>Chemotherapy for low-risk disease should be continued for three cycles of maintenance treatment after hCG normalisation.</td>
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</table>

**Good practice point**
In women with GTN, for whom fertility is not a clinical issue, hysterectomy may be a potential treatment option instead of chemotherapy as initial treatment.
**Clinical question 2.4.3**

For women with high-risk (FIGO ≥7) GTN what is the optimal first-line chemotherapy regimen?

**Evidence statement**

High-risk gestational trophoblastic neoplasia (GTN) is characterised by any one of the following:

- Stage IV disease
- Stage II and III with risk score ≥7.

EMA/CO (etoposide, methotrexate, actinomycin-D plus cyclophosphamide and vincristine) is currently the most widely used first-line combination chemotherapy for high-risk GTN, although this regimen has not been rigorously compared to other combinations such as MAC (methotrexate, actinomycin-D, cyclophosphamide or chlorambucil) or FAV (5-FU, actinomycin D, and vincristine) in randomised controlled trials. Other regimens may be associated with less acute toxicity than EMA/CO; however, proper evaluation of these combinations in high-quality RCTs that include long-term surveillance for secondary cancers is required. Given the low incidence of GTN, RCTs in this field are difficult to conduct, hence multi-centre collaboration is necessary. CHAMOCA (cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan and vincristine) is not recommended for GTN treatment as it is more toxic and not more effective than MAC. (Deng et al., 2013)

A recent retrospective study by Alifrangis et al. (2013) demonstrated that during the period 1995 to 2010, overall survival for all patients with GTN treated with EMA/CO chemotherapy significantly increased from 86.2% before 1995 to 97.9%. EP induction chemotherapy was given to 23.1% of high-risk patients (33 of 140 patients) with a large disease burden, and the early death rate was only 0.7% (n = 1; 95% CI, 0.1% to 3.7%) compared with 7.2% (n = 11 of 151 patients; 95% CI, 4.1% to 12.6%) in the pre-1995 cohort. However, high-risk patients receiving EP, compared with patients not receiving EP, did have a higher but not statistically significant relapse rate (9% v 6%, respectively; P = .44) and death rate (12% v 4%, respectively; P = .088).

**Central nervous system (CNS) prophylaxis**

Charing Cross hospital’s policy is to give prophylaxis to all high-risk patients. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses, which usually coincides with the EMA treatment. In contrast the Sheffield unit only gives CNS therapy to those with proven CNS metastases. They do a brain CT (computed tomography) and a CSF (cerebral spinal fluid) hCG in their ‘high-risk’ patients and only if positive give CNS therapy with intrathecal and intravenous methotrexate. (Charing Cross, 2015)

**Recommendation 2.4.3.1**

<table>
<thead>
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<th>Recommendation 2.4.3.1</th>
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<tbody>
<tr>
<td>Patients with a FIGO score of ≥7 should receive multi-agent chemotherapy and most centres now use EMA/CO, as it is highly effective, easy to administer and relatively non-toxic.</td>
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**Recommendation 2.4.3.2**

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<th>Recommendation 2.4.3.2</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Early deaths in ultra high-risk GTN can be reduced by induction therapy with etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EP/EMA.</td>
<td>C</td>
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</table>

**Good practice point**

For women with high-risk GTN, decisions should be made on an individual patient basis following discussion with clinicians experienced in high-risk GTN management, at national MDT.
Clinical question 2.4.4
For women with low-risk gestational trophoblastic neoplasia undergoing chemotherapy (first-course), what is the recommended course of action for observing and managing bleeding?

Evidence statement
The guideline development group recommends that the first one/two courses of chemotherapy should be administered as an inpatient at a centre with medical oncology, gynaecological services and interventional radiology. Subsequent courses in uncomplicated patients are administered at a medical oncology day ward facility.

If hCG levels are very high, the uterine mass large or there is evidence of vaginal metastases, patients may be kept in for two complete courses or longer due to the risk of haemorrhage (Seckl & Savage, 2012).

Per vaginal or intraperitoneal bleeding can occur. Moderate bleeding usually responds to bed rest and chemotherapy. Torrential bleeding may require treatment with a vaginal pack, blood products, anti-fibrinolytics, emergency embolisation and very rarely with hysterectomy. In Charing Cross experience, less than 1.5% of GTN patients have required one of these interventions over the past 25 years. (Charing Cross, 2015)

<table>
<thead>
<tr>
<th>Recommendation 2.4.4.1</th>
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<tbody>
<tr>
<td>For women with low-risk GTN undergoing first-line chemotherapy, the first ± second courses of chemotherapy should be administered as an in-patient at a centre with medical oncology, gynaecological services and interventional radiology.</td>
<td>C</td>
</tr>
</tbody>
</table>
Clinical question 2.4.5
For women with gestational trophoblastic neoplasia, what are the appropriate investigations to monitor response to chemotherapy and follow-up?

Evidence statement
Monitoring response to chemotherapy – Low-Risk
Patients should have hCG levels monitored twice a week during treatment. Treatment is continued until hCG is normal and then usually for three further courses to eliminate any residual tumour cells and to minimise the chances of relapse. Non-randomised data suggest that reducing the consolidation therapy by just one cycle doubles the risk of relapse (Lybol et al., 2012). (Seckl et al., 2013)

Monitoring response to chemotherapy – High-Risk
Therapy is continued for 6 weeks of normal hCG values or 8 weeks if poor prognostic features such as liver or brain metastases are present. Patients are then re-imaged to document the post-treatment appearance for future comparison. Removal of residual masses is unnecessary as it does not reduce the risk of recurrence which is less than 3% (Seckl et al., 2010). (Seckl et al., 2013)

Follow-up of patients post chemotherapy
After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels. Some centres e.g. Charing Cross, continue bi-annual titers indefinitely for high-risk individuals. Subgroups that might fit into this high-risk category include women with extreme treatment resistance who required multiple regimens of combination therapy, those with advanced stage choriocarcinoma, particularly with chemoresistance, and patients who have late recurrences. (Garner, 2013)

Follow-up for at least 5 years may be considered for those at highest risk.

<table>
<thead>
<tr>
<th>Recommendation 2.4.5.1</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Monitoring during treatment low-risk:</td>
<td></td>
</tr>
<tr>
<td>Patient should have human chorionic gonadotropin (hCG) levels monitored twice a week during treatment.</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation 2.4.5.2</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring during treatment high-risk:</td>
<td></td>
</tr>
<tr>
<td>Patients with high-risk disease should have maintenance therapy for three cycles after hCG normalisation extended to four cycles for patients with poor prognostic features such as liver metastases with or without brain metastases.</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation 2.4.5.3</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up post treatment:</td>
<td></td>
</tr>
<tr>
<td>After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels.</td>
<td>C</td>
</tr>
</tbody>
</table>

Good practice point
Follow-up for at least five years may be considered for those at highest risk.
Clinical question 2.4.6
For women with gestational trophoblastic neoplasia what are the indicators to determine switching treatments from first-line chemotherapy?

Evidence statement
Chemotherapy should continue until hCG returns to normal, and at least three more chemotherapy cycles should be administered after the first normal hCG result (Lybol et al., 2012). The drug in use should be replaced by another when there is an inadequate response i.e. a rise in hCG values over two successive measurements a week apart or a plateau in three successive weekly measurements a week apart or when toxicity (such as mucositis, pleuritic chest pain or abdominal pain) precludes the use of appropriate doses or treatment frequency.

About 5% of patients with low-risk GTN without metastases and 10-15% of those that have metastases develop resistance to first-line chemotherapy (Lurain & Nejad, 2005). (Biscaro et al., 2015)

Resistance to chemotherapy and recurrent disease are more frequent in patients with high-risk GTN (Berkowitz & Goldstein, 2013). About 20-30% of high-risk patients have an incomplete response to first-line chemotherapy or recurrence after remission and eventually need salvage chemotherapy. (Biscaro et al., 2015)

<table>
<thead>
<tr>
<th>Recommendation 2.4.6.1</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients with low-risk GTN the clinical indicators for a change in treatment from first-line chemotherapy include: treatment related toxicity, a rise in hCG values over two successive measurements a week apart or a plateau in three successive weekly measurements a week apart.</td>
<td>C</td>
</tr>
</tbody>
</table>

Good practice point
Consideration could be given to re-staging patients prior to the initiation of a new regimen (particularly high-risk patients).
Clinical question 2.4.7

For women with low-risk gestational trophoblastic neoplasia who have not responded to single-agent treatment (methotrexate or actinomycin D) or have relapsed following normalisation of hCG after completion of single-agent treatment, what is the next line of treatment?

Evidence statement

The next line of treatment is determined by the patient’s current hCG levels, with those with hCG levels <300 IU/l receiving single-agent Actinomycin-D and those with hCG levels of >300 IU/l commencing on EMA–CO (Seckl et al., 2013).

In a recent study, Sita-Lumsden et al. (2012) demonstrated that a higher cut-off value of 300 IU/l produced an overall second-line actinomycin-D success rate of 94% that compares favourably with the 87% reported when the cut-off value was 100 IU/l.

For women with low-risk GTN if sequential single-agent therapy fails, multi-agent chemotherapy must be used to achieve a cure; this is necessary in 6% to 15% of cases (Covens et al., 2006; Goldstein & Berkowitz, 2012). The multi-agent therapy used most frequently at Charing Cross (one of two treatment centres in the UK) is EMA/CO. The New England Trophoblastic Disease Centre (NETDC, USA) prefers to use MAC before EMA/CO owing to concerns that etoposide may be associated with an increased risk of secondary tumours (Goldstein & Berkowitz, 2012). (Alazzam, 2012)

In Ireland it is current practice to use EMA/CO as first-line combination therapy. Patients should be treated under the care of a medical oncologist with experience in the treatment of GTN.

A recent retrospective study demonstrated an overall survival rate of 99.6%, in 250 low-risk patients who received second-line EMA/CO after relapse or resistance to single-agent chemotherapy. Four patients (1.5%) developed resistance and/or experienced relapse after EMA/CO. These patients were all cured with further salvage regimens (Alifrangis et al., 2013).

Central nervous system (CNS) prophylaxis

Charing Cross hospital’s policy is to give prophylaxis to all high-risk patients and to the low-risk patients with lung metastases. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses. For the high-risk patients it usually coincides with the EMA treatment. In contrast the Sheffield unit only gives CNS therapy to those with proven CNS metastases. They do a brain CT scan and measure CSF hCG in their ‘high-risk’ patients and only if positive give CNS therapy with intrathecal and intravenous methotrexate (Charing Cross, 2015).

<table>
<thead>
<tr>
<th>Recommendation 2.4.7.1</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>For women with low-risk GTN who have not responded or have relapsed from single-agent treatment (methotrexate or actinomycin D), the next line of treatment is combination chemotherapy with EMA/CO.</td>
<td>B</td>
</tr>
</tbody>
</table>
Clinical question 2.4.8
For women with high-risk GTN who have not responded or have relapsed from first-line treatment, what is second-line of treatment?

Evidence statement
In women with high-risk GTN who have not responded or have relapsed from first-line treatment, consideration should be given to discussing each individual case with an international expert due to the rarity of this condition.

Currently, the most commonly used salvage regimen in North America and the UK for the treatment of resistant or recurrent high-risk GTN is EMA/EP (May et al., 2011). A Cochrane review demonstrated that approximately 90% of high-risk patients treated initially with EMA/CO, followed by salvage therapy with a platinum-etoposide combination if required, will survive (Lurain 2010). In three series of EMA/EP salvage treatment following EMA/CO treatment failure, cure rates of 75% (nine out of 12 women; Newlands 2000) 66.6% (12 out of 18 women; Mao 2007) and 84.9% (11 out of 13 women; Lu 2008) were reported; however, EMA/EP was associated with significant myelosuppression and hepatotoxicity, leading to treatment delays and dose reductions. Myelosuppression may be minimised by administering granulocyte-colony stimulating factor (G-CSF) (El-Helw 2005; Lurain 2005; Seckl 2010). (Alazzam et al., 2012)

An alternative to EP/EMA is TE/TP (paclitaxel/cisplatin and paclitaxel/etoposide). The taxane-containing regimen was found to be associated with comparable cure rates to EMA/EP (70% of 10 patients who had not been exposed to previous EP treatment were cured) but with relatively reduced toxicity and no dose delays or reductions (Alazzam et al., 2012). A randomised trial comparing these regimens is being developed (Seckl et al., 2013).

Another approach in patients with refractory disease involves high-dose chemotherapy with peripheral stem-cell transplantation. Cures are not common (El-Helw et al., 2005). (Seckl et al., 2013)

This approach should only be undertaken after expert advice has been sought internationally.

Central nervous system (CNS) prophylaxis
Charing Cross hospital’s policy is to give prophylaxis to all high-risk patients and to the low-risk patients with lung metastases. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses. For the high-risk patients it usually coincides with the EMA treatment. In contrast the Sheffield unit only gives CNS therapy to those with proven CNS metastases. They do a brain CT scan and measure CSF hCG in their ‘high-risk’ patients and only if positive give CNS therapy with intrathecal and intravenous methotrexate (Charing Cross, 2015).

Recommendation 2.4.8.1
For women with high-risk GTN who have not responded or have relapsed from first-line treatment, acceptable regimens include EP/EMA and TE/TP.

Grade C

Good practice point
Given the rarity of this condition consideration should be given to discussing each individual case with international experts.
Clinical question 2.4.9
For women with GTN, who are acutely ill with liver, brain or lung metastasis at presentation, what is the optimum chemotherapy regimen?

Evidence statement
Given the rarity of this condition consideration should be given to discussing each individual case with international experts.

Emergency treatment
In patients who are acutely unwell from liver or CNS (central nervous system) disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP. This can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point. (Charing Cross, 2015)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Etoposide 100mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cisplatin 20mg/m²</td>
</tr>
<tr>
<td>Day 2</td>
<td>Etoposide 100mg/m²</td>
</tr>
<tr>
<td></td>
<td>Cisplatin 20mg/m²</td>
</tr>
</tbody>
</table>

Hepatic metastases
Patients with hepatic metastases at presentation should commence therapy using EP/EMA protocol. (Charing Cross, 2015)

Research by Barber et al. (2014) on patients with hepatic metastases revealed that 82% experienced a complete response to EMA/CO versus only 17% experiencing a complete response to other types of chemotherapy (Methotrexate, ACT-D, or MAC) (P = 0.035).

Cerebral metastases
The Charing Cross hospital’s treatment for this is the high dose EMA/CO, using an increased methotrexate dose (1gm/m²) combined with longer folinic acid (FA) rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the human chorionic gonadotropin (hCG) normalisation. Intrathecal methotrexate is also given as 12.5mg +15mg FA on the CO week until serum hCG is normal at which point it is discontinued.

In emergency situations with cerebral metastases, hi-dose dexamethasone is given followed by two day EP as above. (Charing Cross, 2015)

Hepatic and synchronous cerebral metastases
In patients with liver and brain metastases the treatment used should be as follows:

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Day 1</th>
<th>Actinomycin-D 0.5mg IV (flat dose not m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Etoposide 100mg/m² IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal saline 1000ml + 20mMol KCl over 2hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate 1000mg/m² in 1000ml normal saline over 24hrs IV</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>Folinic acid 30mg po 6 hourly x 12 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Starting 32hrs after commencing methotrexate</td>
</tr>
<tr>
<td>Week 2</td>
<td>Day 8</td>
<td>Etoposide 150mg/m² IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin 75mg/m² IV</td>
</tr>
</tbody>
</table>
This combines the EMA (CNS) dose with the EP treatment. It misses out the day two of the normal EMA protocol as it is too myelosuppressive when combined with EP to allow for this. We would use G-CSF (granulocyte – colony stimulating factor) for 3-4 days every week in between day 1 and 8 and day 8 and 1.

Intrathecal methotrexate is also given 12.5mg + 15mg FA on the EP week until serum hCG is normal at which point it is discontinued (Charing Cross, 2015, Savage et al., 2015).

**Respiratory failure**

In patients with large volume pulmonary lung metastases oxygen support can be given but ventilation is contraindicated, due to the risk of traumatic haemorrhage from the tumour vasculature.

Respiratory compromise can also result from tumour within the pulmonary vasculature. This can respond promptly to chemotherapy. Consideration can be given to anti-coagulation in these rare patients with tumour emboli. (Charing Cross, 2015)

<table>
<thead>
<tr>
<th>Recommendation 2.4.9.1</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency treatment</td>
<td>C</td>
</tr>
</tbody>
</table>
In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m\(^2\) D1+2, P 20mg/m\(^2\) D1+2). This can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point.

<table>
<thead>
<tr>
<th>Recommendation 2.4.9.2</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic metastases</td>
<td>C</td>
</tr>
</tbody>
</table>
In patients who are acutely unwell from liver disease emergency chemotherapy can be started with two day EP (E 100mg/m\(^2\) D1+2, P 20mg/m\(^2\) D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. Patients with hepatic metastases at presentation should commence therapy using EP/EMA protocol. Given the rarity of this condition each individual case should be discussed with international experts.

<table>
<thead>
<tr>
<th>Recommendation 2.4.9.3</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral metastases</td>
<td>C</td>
</tr>
</tbody>
</table>
In patients who are acutely unwell from CNS emergency chemotherapy can be started with two day EP (E 100mg/m\(^2\) D1+2, P 20mg/m\(^2\) D1+2). This can be repeated weekly and then altered to high dose EMA/CO at a later point using an increased methotrexate dose (1gm/m\(^2\)) combined with longer FA rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the hCG normalisation. In emergency situations with cerebral metastases, hi-dose dexamethasone is given followed by two day EP as above. Given the rarity of this condition each individual case should be discussed with international experts.

<table>
<thead>
<tr>
<th>Recommendation 2.4.9.4</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic and synchronous cerebral metastases</td>
<td>C</td>
</tr>
</tbody>
</table>
In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure, emergency chemotherapy can be started with two day EP (E 100mg/m\(^2\) D1+2, P 20mg/m\(^2\) D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. This combines the EMA (CNS) dose with the EP treatment. It misses out the day two of the normal EMA protocol as it is too myelosuppressive when combined with EP to allow for this. Given the rarity of this condition each individual case should be discussed with international experts.
Appendix 1: Epidemiology of GTD

Incidence
Estimates for the incidences of GTD vary around the world. In the USA, the incidence of molar pregnancy is deemed to be 1/1,500 live births, while in the United Kingdom, the incidence is estimated at 1/714 live births. In general, North American and European countries tend to report low or intermediate rates of disease (1 per 1,000 to 1,500 pregnancies), whereas Asian and Latin American nations often have higher rates (1 in 12 to 500 pregnancies) (Goldstein et al., 2014). This is supported by evidence in the UK of ethnic variation, with higher incidence rates among Asian women (1/387 live births) (Kumar & Kumar, 2011).

Epidemiological data is limited by the rarity of the disease and inaccurate recording of data in relation to the number of gestational events (Goldstein et al., 2014). It has been argued that regional variation results from problems in reporting as well as socioeconomic and nutritional factors. The problems in reporting reliable epidemiological data can be attributed to a number of factors such as - reporting population-based versus hospital-based data, inconsistencies in case definitions, inability to adequately characterise the population at risk, lack of centralised databases, and insufficiently chosen control groups against which to compare possible risk factors (Lurain 2012). The incidence is very difficult to measure as not all cases will be reported or recognised and there is currently no database that records gestational events in the Irish population.

In the UK, GTD services have been centralised to two hospitals, Charing Cross and Sheffield, for the last 40 years. Centralisation of services has served to concentrate patient care with sufficient patient numbers to allow for the optimisation of protocols for treatment and surveillance. Additionally, it has facilitated registration of patients providing a central database that is used for research and audit purposes. In Ireland, data on incidences of GTD comes from the Hospital In-Patient Enquiry (HIPE) system. In 2013, there were 195 discharges with a primary diagnosis of hydatidiform mole, malignant neoplasm of placenta, or neoplasm of placenta of uncertain origin to hospitals in the Irish public system. It is estimated that approximately 86 patients gave rise to the 195 discharges – this estimate is calculated by deduplicating discharges to hospital with the same medical record number. However, this estimate is likely to be an over estimate as the lack of a unique identifier makes tracking patients across hospitals impossible in the HIPE system. So any patient that was diagnosed in one hospital and retreated in another is likely to be double counted.

![Figure 5](image_url)  
Figure 5 Estimates of the numbers of patients diagnosed with GTD (excluding private hospitals)
Leaving aside concerns regarding the accuracy of the absolute numbers of patients, trends across time should be robust. Figure 5 shows that in Ireland the incidence of GTD appears to be stable between 2005 and 2013. On average, 105 new cases of GTD were diagnosed annually between 2005 and 2013. The rise seen between 2005 and 2009 is consistent with the change in birth rate during this period (CSO, 2013).

**Risk factors**

Important risk factors in developing a molar pregnancy include maternal age and a previous history of GTD (Goldstein et al., 2014). Women over the age of 40 years are 5-10 times more likely to develop CHM, while one third of pregnancies in women above the age of 50 years results in molar gestation. Partial hydatidiform mole (PHM) appears to be common in women with a history of irregular menses and the use of oral contraceptives for more than 4 years (Kumar & Kumar, 2011). Other factors that appear to increase the risk of a molar pregnancy include infertility and diet (McGee & Covens, 2012).

**Mortality/Survival**

Despite the potentially serious outcome of malignant GTN, most women with all forms of GTD can be successfully diagnosed and treated, with preservation of their normal reproductive function (Soper, 2006). The outcome for more than 98% of women with GTN is excellent, however a small number of women will die from the disease, mainly due to late presentation and diagnosis or drug resistance (Seckl et al., 2010). The overall survival rate in patients with GTN treated at the John I. Brewer Trophoblastic Disease Centre in Chicago improved from 88.6% in 1962-1978 to 97.8% in 1979-2006. (Hoekstra et al., 2008). Similarly a study carried out in Charing Cross Hospital between 2000-2009 showed that in the setting of a formal follow-up programme, the expected cure rate for patients with GTN should be ~ 100%. Of their 618 treated patients, 97% were cured after initial curative treatment, 3% relapsed and required further treatment (Sita-Lumsden et al., 2012).

**Subsequent pregnancy**

The most common concern patients express when diagnosed with molar pregnancy or GTN is in relation to the effect of the disease on future reproductive function. (Goldstein & Berkowitz, 2012)

- **Pregnancy after complete and partial hydatidiform mole**
  - Despite an increased risk for developing a second molar pregnancy, patients with molar pregnancies can anticipate normal reproduction in the future. (Goldstein & Berkowitz, 2012)

- **Pregnancy after Gestational Trophoblastic Neoplasia**
  - Patients who are treated successfully with chemotherapy can also generally experience normal reproductive function. (Goldstein & Berkowitz, 2012)
Appendix 2: NCCP Guideline Development Group membership

Terms of reference
To develop a national evidence-based clinical guideline for the diagnosis, staging and treatment of patients with GTD. Full terms of reference are available in the NCCP Methodology Manual for guideline development.

Membership of the Guideline Development Group

Chair
Ms. Noreen Gleeson  Consultant Gynaecological Oncologist, SJH & The Coombe Women’s Hospital

Members
Mr. John Coulter  Consultant Obstetrician/Gynaecologist, CUMH
Dr. Dearbhaile O’Donnell  Consultant Oncologist, SJH
Dr. Paula Calvert  Consultant Medical Oncologist, WRH
Prof. Seamus O’Reilly  Consultant Medical Oncologist, CUMH (until Jan 2015)
Ms. Catherine Duffy  Co-Project Manager, GTD Tumour Group, NCCP
Ms. Ruth Ryan  Co-Project Manager, GTD Tumour Group, NCCP
Dr. Eve O’Toole  Guideline Methodologist, NCCP
Mr. Brendan Leen  Regional Librarian, HSE South East

Conflict of interest
Members declared no conflicts of interest.

Additional contributors:

NCCP Research Staff
Ms. Deirdre Faherty  Senior Research Officer
Ms. Louise Murphy  Research Officer

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Ms. Niamh O’Rourke  Project Manager, NCCP (until Jan 2015)
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Dr. Conor Teljeur  Senior Statistician, HIQA
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Ms. Clare Meaney  Pharmacist, NCCP
Ms. Hilary Murphy  Nurse Specialist, NCCP
Ms. Juliet Kelly  Network Lead Radiation Therapy, NCCP (deceased 2013)
Acknowledgments

Dr. Jerome Coffey          National Director, NCCP
Dr. Mary Hynes            Deputy Director, NCCP
Dr. Susan O’Reilly        Director, NCCP (until Nov 2014)
Prof. Mike Clarke         Director of MRC Methodology Hub, QUB
Mr. Robin Harbour         Lead Methodological, SIGN

Charing Cross Hospital
Royal College of Obstetricians and Gynaecologists (RCOG)
European Society for Medical Oncology (ESMO)
Appendix 3: NCCP Guideline Steering Group membership

Terms of reference
To set strategic direction regarding the development of multidisciplinary/interdisciplinary evidence-based clinical practice guidelines for the diagnosis, staging and treatment of cancer. Full terms of reference are available in the NCCP Guideline Methodology Manual for guideline development.

Membership of the NCCP Guideline Steering Group
The NCCP Guideline Steering Group provided governance for the development of the guideline. The members of the steering group are listed below. The GDG project managers were also present at meetings as observers.

Chair
Dr. Jerome Coffey National Director, NCCP
Dr. Susan O’Reilly National Director, NCCP (until Nov 2014)

Members
Mr. Justin Geoghegan Chair Hepatobiliary GI GDG, SVUH
Ms. Noreen Gleeson Chair Gynaecological GDG, SJH & The Coombe Women’s Hospital
Dr. Mary Hynes Deputy Director, NCCP
Prof. Arnold Hill NCCP Surgical Oncology Advisor
Dr. Maccon Keane NCCP Medical Oncology Advisor
Dr. Marcus Kennedy Chair Lung GDG, CUH
Mr. Brendan Leen Regional Librarian HSE South-East
Ms. Debbie McNamara Chair Lower GI GDG, BH
Dr. Deirdre Murray Health Intelligence, NCCP
Dr. Ann O’Doherty Chair Breast GDG, SVUH
Dr. Margaret O’Riordan Medical Director, ICGP (to May 2014)
Dr. Eve O’Toole Guideline Methodologist, NCCP
Mr. David Quinlan Chair Prostate GDG, SVUH
Prof. John Reynolds Chair Gastrointestinal GDG, SJH
Dr. Karen Ryan Consultant in Palliative Medicine & Clinical Lead Clinical Programme for Palliative Care, SFH

Patients: The views and preferences of the target population were sought by inviting patient advocacy groups to engage in the national stakeholder review process (NCCP Methodology: Appendix VII) and also in the development of information materials.

Management: A Cancer Network Manager from the NCCP meets with each cancer centre (CEO/General Manager) on a quarterly basis for performance monitoring and service planning. A lead clinician for Gynaecology Oncology is nominated in each cancer centre.
### Appendix 4: Clinical questions in PICO format

#### Diagnosis

<table>
<thead>
<tr>
<th>Clinical question 2.2.1</th>
<th>Should all women undergoing medical management of miscarriage have histopathology of products of conception to exclude trophoblastic disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Women undergoing medical management of miscarriage</td>
</tr>
<tr>
<td><strong>Intervention:</strong></td>
<td>Histopathology of products of conception</td>
</tr>
<tr>
<td><strong>Comparison:</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>Outcome:</strong></td>
<td>To identify partial or complete molar pregnancy</td>
</tr>
</tbody>
</table>

**Clinical question 2.2.2**  
For women with suspected molar pregnancy, what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?

| **Population:**         | Women with suspected molar pregnancy                                                                                        |
| **Intervention:**       | Diagnostic tests                                                                                                           |
| **Comparison:**         | -                                                                                |
| **Outcome:**            | Accurately diagnose partial/complete molar pregnancy - sensitivity and specificity                                            |

**Clinical question 2.2.3**  
For women where there is suspicion of partial or complete molar pregnancy who have an evacuation performed, in what time frame should the pathology report (post-evacuation) be available to the clinician?

| **Population:**         | Women with suspected partial or complete molar pregnancy                                                                  |
| **Intervention:**       | Histopathological review                                                                                                  |
| **Comparison:**         | -                                                                                |
| **Outcome:**            | Time to report to clinician                                                                                               |

**Clinical question 2.2.4**  
For women with gestational trophoblastic disease should management be centralised to a specialised centre(s) to ensure optimum outcome?

| **Population:**         | Women with confirmed GTD                                                                                                  |
| **Intervention:**       | Registration and central advice                                                                                         |
| **Comparison:**         | -                                                                                |
| **Outcome:**            | Optimum outcomes - early appropriate management - improved overall survival - protocol-driven systemic therapy administration |

**Clinical question 2.2.5**  
For women with partial and complete molar pregnancy, what clinical and human chorionic gonadotropin monitoring protocol should be carried out to ensure they have been fully followed up and require no further therapy or monitoring?

| **Population:**         | Women with partial or complete molar pregnancy                                                                         |
| **Intervention:**       | Monitoring investigation – hCG levels                                                                                   |
| **Comparison:**         | -                                                                                |
| **Outcome:**            | Do not require further therapy or monitoring                                                                            |
Staging

Clinical question 2.3.1
For women with Gestational Trophoblastic Neoplasia (GTN), what investigations should be done to accurately stage GTN?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with confirmed GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Chest X-ray (CXR), liver ultrasound (US), transvaginal ultrasound (TVU), Magnetic Resonance Imaging (MRI) brain (if Lung metastases), Computed Tomography – Thorax, Abdomen and Pelvis (CT-TAP) (if abnormality on chest x-ray or liver ultrasound)</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>To determine extent of disease</td>
</tr>
<tr>
<td></td>
<td>To determine chemotherapy regimen</td>
</tr>
</tbody>
</table>

Clinical question 2.3.2
For women with gestational trophoblastic neoplasia (GTN), what risk scoring system should be used to stage GTN?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with confirmed GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Staging system</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Accurate staging of GTN</td>
</tr>
</tbody>
</table>
# Treatment

## Clinical question 2.4.1
For women with malignant gestational trophoblastic neoplasia, what are the clinical indicators to diagnose GTN warranting chemotherapy?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Clinical indicators</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Commencement of chemotherapy</td>
</tr>
</tbody>
</table>

## Clinical question 2.4.2
For patients with low-risk (FIGO 0-6) GTN, what is the optimal first-line chemotherapy regimen?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with GTN</th>
</tr>
</thead>
</table>
| Intervention: | Chemotherapy regimens  
- Methotrexate / Folinic Acid  
- Actinomycin D |
| Comparison: | - |
| Outcome: | 5-year survival  
Recurrence  
Metastases  
Side-effects from chemotherapy  
Toxicity |

## Clinical question 2.4.3
For women with high-risk (FIGO ≥7) GTN what is the optimal first-line chemotherapy regimen?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with GTN</th>
</tr>
</thead>
</table>
| Intervention: | Chemotherapy regimens  
- EMA-CO  
- EP/EMA chemotherapy  
- TE/TP chemotherapy |
| Comparison: | - |
| Outcome: | 5-year survival  
Recurrence  
Metastases |

## Clinical question 2.4.4
For women with low-risk gestational trophoblastic neoplasia undergoing chemotherapy (first-course), what is the recommended course of action for observing and managing bleeding?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with GTN undergoing chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Observation &amp; management of bleeding</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Optimum management</td>
</tr>
</tbody>
</table>

## Clinical question 2.4.5
For women with gestational trophoblastic neoplasia, what are the appropriate investigations to monitor response to chemotherapy and follow-up?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>hCG levels</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Response to chemotherapy and follow-up</td>
</tr>
</tbody>
</table>
Clinical question 2.4.6
For women with low-risk gestational trophoblastic neoplasia what are the indicators to determine switching treatments from first-line chemotherapy?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with low-risk GTN undergoing first-line chemotherapy</th>
</tr>
</thead>
</table>
| Intervention: | Indicators  
  - plateau in hCG  
  - toxicity |
| Comparison: | - |
| Outcome: | Switch from first-line treatment |

Clinical question 2.4.7
For women with low-risk gestational trophoblastic neoplasia who have not responded or have relapsed from single-agent treatment (methotrexate or actinomycin D) or have relapsed following normalisation of hCG after completion of single-agent treatment, what is the next line treatment?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with low-risk invasive GTN who have not responded to single-agent treatment or relapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Next line treatment chemotherapy</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>5-year survival</td>
</tr>
</tbody>
</table>

Clinical question 2.4.8
For women with high-risk GTN who have not responded or have relapsed from first-line treatment, what is second-line treatment?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with high-risk GTN who have not responded to first-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Second-line treatment chemotherapy</td>
</tr>
<tr>
<td>Comparison:</td>
<td>-</td>
</tr>
<tr>
<td>Outcome:</td>
<td>5-year survival</td>
</tr>
</tbody>
</table>

Clinical question 2.4.9
For women with GTN, who are acutely ill with liver, brain or lung metastasis at presentation, what is the optimum chemotherapy regimen?

<table>
<thead>
<tr>
<th>Population:</th>
<th>Women with GTN who are acutely ill with liver, brain or lung metastasis</th>
</tr>
</thead>
</table>
| Intervention: | Management/treatment options  
  - 2 days EP (Charing Cross protocol) |
| Comparison: | - |
| Outcome: | Survival |
## Appendix 5: Systematic literature review protocol

**SYSTEMATIC LITERATURE REVIEW PROTOCOL**

Literature searches to answer clinical questions identified by the relevant guideline development group will be conducted using the following procedure. Questions should only be submitted if they have not been adequately answered in the guidelines adopted by the guideline development group, or where guidelines need to be updated. Guidelines should be identified in consultation with library services.

<table>
<thead>
<tr>
<th>GDG</th>
<th>PICO(T)</th>
<th>GDG/Library Services</th>
<th>Question Category</th>
<th>Library Services</th>
<th>Literature Search</th>
<th>Other Database</th>
<th>Other Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Cochrane Library | 3.1 | Analyse the clinical question using PICO(T) and complete a Clinical Query Request form.
| See below Annex 1: Clinical Query Request. | | Assign a question category, if appropriate: Therapy/Intervention, Aetiology/Risk Factors, Diagnosis, Prognosis/Prediction, Frequency/Rate, Phenomena, Other.
| | | Conduct searches of the following bibliographic databases in the order specified below using keywords implicit in the PICO(T) strategy and any identified subject headings:
| | | 3.1 Cochrane Library
| | | Comprising: the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials (Central); the Database of Abstracts of Reviews of Effects; the Health Technology Assessment Database; the NHS Economic Evaluation Database.
| | | Use MeSH and keyword searches to identify systematic reviews and other relevant studies.
| | | 3.2 Point-of-Care Reference Tools
| | | One or more of the following point-of-care reference tools: BMJ Best Practice; DynaMed; UpToDate.
| | | 3.3 Medline
| | | Use MeSH and keyword searches. Limit results using the ‘Human’ search filter. Unless otherwise specified by the guideline development group or warranted by the specific clinical question, limit results to studies from the previous five years. Where appropriate, limit intervention questions according to the following priority: Medline clinical queries; Cochrane systematic reviews; other systematic reviews or meta-analyses; RCTs; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources.
| | | Where appropriate, limit diagnosis, prognosis or aetiology questions according to the following priority: Medline clinical queries; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources.
| | | 3.4 Embase
| | | Repeat the Medline search strategy above using Embase, if available.
| | | 3.5 Other Bibliographic Databases
| | | Repeat the Medline search strategy above using the Cumulative Index to Nursing and Allied Health Literature and/or PsycINFO, as appropriate.
| | | 3.6 Other Sources
| | | Use any other sources for background or additional information, as appropriate. Other sources may include: PubMed, particularly for in-process or ahead-of-print citations; quality-assured, subject-specific Internet resources; clinical reference books; patient information materials; etc.
| | | | | | | | |

---

**GDG**

A National Clinical Guideline

**Diagnosis, staging and treatment of patients with gestational trophoblastic disease**

HSE Library Services

NCCP Guideline Development

www.hselibrary.ie
3.7 Trial Registers

When a relevant trial is identified through searching the bibliographic databases, a search of trial registers should be carried out to identify any related trials which have been completed but whose findings have not been published or made available. The guideline development group should be alerted to the presence of these unpublished trials. The following sources may be included:

3.7.1 ClinicalTrials.gov: http://clinicaltrials.gov/

3.7.2 Cochrane Central Register of Controlled Trials (Central): http://www.thecochranelibrary.com/

3.7.3 EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/

3.7.4 International Prospective Register of Systematic Reviews (Prospero): http://www.crd.york.ac.uk/prospero/search.asp

3.7.5 WHO International Clinical Trials Registry: http://apps.who.int/trialsearch/

3.8 For questions relating to economic evaluations, use the SIGN economic studies filter for Medline as a basis for the search strategy: http://www.sign.ac.uk/methodology/filters.html#econ.

The following source may also be consulted, if available:


Retain an electronic record of the search strategy and all search results using the Zotero reference management utility.

Respond to the guideline development group using the Clinical Query Response form to include:

- a copy of the search strategy
- bibliographic details of all search results identified
- optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question

See below Annex 2: Clinical Question Response.

6.1 Set up an alert to review results lists returned to the guideline development group to rapidly capture any articles that are subsequently retracted or withdrawn, and notify the guideline development group accordingly.

6.2 Review all articles included in recommendations of the completed guideline to confirm that they have not been subsequently retracted or withdrawn.

A summary of the search strategy is included as an addendum to the completed guideline. Complete the Clinical Question: Summary of Search Strategy form and return to the guideline development group. See below Annex 3: Clinical Question: Summary of Search Strategy.

Once internal review of the guideline has been completed, literature searches for all clinical questions should be updated to capture articles published in the interim between the original literature search and the final draft of the guideline. Updated literature searches should be conducted prior to submission of the guideline for external review.

Respond to the guideline development group as previously using the Clinical Query Response form to include:

- a copy of the search strategy
- bibliographic details of all search results identified
- optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question

See below Annex 2: Clinical Question Response.
# ANNEX 1

## CLINICAL QUESTION REQUEST TO LIBRARY

### Your Contact Details

<table>
<thead>
<tr>
<th>Name</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Job Title</td>
<td></td>
</tr>
<tr>
<td>Work Address</td>
<td></td>
</tr>
<tr>
<td>Telephone</td>
<td></td>
</tr>
<tr>
<td>Email</td>
<td></td>
</tr>
<tr>
<td>Employee Number</td>
<td></td>
</tr>
</tbody>
</table>

Please state your clinical question

... and list any relevant keywords

... or (optional) enter keywords under the following headings (PICO)

#### PICO

- **Population/Problem**
- **Intervention/Indicator**
- **Comparator/Control**
- **Outcome**

Is your question specific to any of the categories below?

<table>
<thead>
<tr>
<th>GENDER</th>
<th>AGE GROUP</th>
<th>DATE OF PUBLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Infant (0–23months)
- Child (2–12years)
- Adolescent (13–18years)
- Adult (19–65years)
- Aged (>65years)

Current year only

- 0–5 years
- >5 years

### Question Type

- Therapy/Intervention
- Aetiology/Risk Factors
- Diagnosis
- Prognosis/Prediction
- Frequency/Rate
- Phenomena
- Other

### Additional Information
Dear ____________.

Thank you for your email. Please see attached in response to your clinical query and, below, details of the search strategy applied to your question. If you wish to source any of the references contained in these results, or to search further, please do not hesitate to contact us.

Best wishes,

______________.

[ATTACH CLINICAL QUESTION REQUEST HERE]

<table>
<thead>
<tr>
<th>Search Strategy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Database(s) Searched</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Search Strategy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Other/Secondary Resources Searched</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Contact**

| Your Library Staff Contact |  |
| Date |  |
## ANNEX 3

### CLINICAL QUESTION: SUMMARY OF SEARCH STRATEGY

<table>
<thead>
<tr>
<th>Clinical Question</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PICO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population/Problem</td>
</tr>
<tr>
<td>Intervention/Indicator</td>
</tr>
<tr>
<td>Comparator/Control</td>
</tr>
<tr>
<td>Outcome</td>
</tr>
</tbody>
</table>

Is your question specific to any of the categories below?

<table>
<thead>
<tr>
<th>GENDER</th>
<th>AGE GROUP</th>
<th>DATE OF PUBLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Infant (0 – 23 months)</td>
<td>Current year only</td>
</tr>
<tr>
<td>Female</td>
<td>Child (2 – 12 years)</td>
<td>0 – 5 years</td>
</tr>
<tr>
<td></td>
<td>Adolescent (13 – 18 years)</td>
<td>&gt; 5 years</td>
</tr>
<tr>
<td></td>
<td>Adult (19 – 65 years)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aged (&gt; 65 years)</td>
<td></td>
</tr>
</tbody>
</table>

Question Type

- Therapy/Intervention
- Aetiology/Risk Factors
- Diagnosis
- Prognosis/Prediction
- Frequency/Rate
- Phenomena
- Other

Search Strategy

- Primary Database(s) Searched
- Search Strategy: [Copy of base Medline and/or PubMed search strategy HERE. Include subject headings and search hits].
- Other/Secondary Resources Searched
- Search Strategy: Other Resources: [Copy of other search strategies HERE. Include subject headings and search hits].
- Comments: [Short paragraph describing search].
- Date
ANNEX 4
SYSTEMATIC LITERATURE REVIEW WORKFLOW*

STEP 1
IDENTIFYING GAPS IN EXISTING CLINICAL GUIDELINES

STEP 2
FORMULATE CLEARLY DEFINED CLINICAL QUESTIONS

STEP 3
SEARCH LITERATURE USING KEYWORDS IMPLICIT IN
PICO(T) AND ANY IDENTIFIED SUBJECT HEADINGS

SEARCH STRATEGY
Retain copy of search strategy and include as appendix (“Summary of Search Strategy”) in completed guideline.

STEP 4
CRITICALLY APPRAISE SEARCH RESULTS

Is evidence sufficient to answer clinical question?

STEP 5
RECOMMENDATIONS
Recommendations should incorporate:
• expert opinion
• patient values
• cost implications


Protocol designed by the HSE/hospital librarians in conjunction with the NCCP.
Appendix 6: Levels of evidence and grading systems

Table 4 Levels of evidence for diagnostic studies (Oxford CEBM, 2009)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic review (with homogeneity*) of Level 1 diagnostic studies; clinical decision rule (CDR&quot;) with 1b studies from different clinical centres.</td>
</tr>
<tr>
<td>1b</td>
<td>Validating** cohort study with good reference standards&quot;&quot;&quot;&quot;; or CDR tested within one clinical centre.</td>
</tr>
<tr>
<td>1c</td>
<td>Absolute SpPins (specificity) and SnNouts (sensitivity)&quot;&quot;&quot;&quot;.</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review (with homogeneity*) of Level &gt;2 diagnostic studies.</td>
</tr>
<tr>
<td>2b</td>
<td>Exploratory** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review (with homogeneity*) of 3b and better studies.</td>
</tr>
<tr>
<td>3b</td>
<td>Non-consecutive study; or without consistently applied reference standards.</td>
</tr>
<tr>
<td>4</td>
<td>Case-control study, poor or non-independent reference standard.</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.</td>
</tr>
</tbody>
</table>

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

** Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into “derivation” and “validation” samples.

Table 5 Grades of recommendations for diagnostic studies (Oxford CEBM, 2009)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Consistent level 1 studies.</td>
</tr>
<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.</td>
</tr>
<tr>
<td>C</td>
<td>Level 4 studies; or Extrapolations from level 2 or 3 studies.</td>
</tr>
<tr>
<td>D</td>
<td>Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.</td>
</tr>
</tbody>
</table>

Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.
### Table 6
Levels of evidence for interventional studies (SIGN grading system 1999-2012)

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.</td>
</tr>
<tr>
<td>1+</td>
<td>Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias.</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies.</td>
</tr>
<tr>
<td></td>
<td>High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.</td>
</tr>
<tr>
<td>2+</td>
<td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies (e.g. case reports, case series).</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion.</td>
</tr>
</tbody>
</table>

### Table 7
Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or</td>
</tr>
<tr>
<td></td>
<td>A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or</td>
</tr>
<tr>
<td></td>
<td>Extrapolated evidence from studies rated as 1++ or 1+.</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or</td>
</tr>
<tr>
<td></td>
<td>Extrapolated evidence from studies rated as 2++.</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or</td>
</tr>
<tr>
<td></td>
<td>Extrapolated evidence from studies rated as 2+.</td>
</tr>
</tbody>
</table>

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

**Good practice point**

Appendix 7: National stakeholder and international expert reviewers

| Clinical leaders and healthcare managers | National Clinical Leads group  
Masters and Obstetrics and Gynaecology Leads in the Maternity Hospitals  
HSE Clinical Programme in Surgery  
HSE Clinical Programme in Pathology  
HSE Clinical Programme in Radiology  
HSE Clinical Programme in Palliative Care  
HSE Clinical Programme in Medicines Management & Pharmacological Interventions  
HSE Clinical Programme in Primary Care  
HSE Clinical Programme in Obstetrics & Gynaecology  
CEOs of the designated Cancer Centres |
|----------------------------------------|-----------------------------------------------------------------------------------|
| National groups, organisations, faculties & committees | Faculty of Surgery, RCSI  
Faculty of Radiology, RCSI  
All Ireland Institute of Hospice and Palliative Care  
The Irish Hospice Foundation  
The Irish Association for Palliative Care  
Irish Society for Medical Oncologists (ISMO)  
Irish Association for Nurses in Oncology (IANO)  
Irish College of General Practitioners (ICGP)  
Irish Association of Directors of Nursing and Midwifery  
Institute of Obstetricians & Gynaecologists, RCPI  
Hospital Pharmacists Association of Ireland  
Oncology Pharmacists Special Interest Group  
Irish Association of Emergency Medicine  
Chairs of Obstetrics and Gynaecology (UCHG, CUH, Trinity, UL) |
| Patient support and advocacy groups | HSE Patient Forum  
Irish Cancer Society  
Cancer Care West  
Marie Keating Foundation  
Gary Kelly Cancer Support Centre  
Bray Cancer Support Centre  
The Miscarriage Association of Ireland |
| International Expert Review | Prof. Michael Seckl, Charing Cross Hospital  
Prof. Francois Golfier, Université Claude Bernard LYON |

The following individuals responded to the stakeholder review and submissions were discussed with the clinical members of the GDG:

- Prof. Michael Turner (Professor of Obstetrics and Gynaecology, The Coombe Women’s Hospital)
- Prof. Conor O’Keane (Clinical Director, Mater Misericordiae University Hospital)
- Dr. John Stratton (Consultant Obstetrician/Gynaecologist, WRH)
- Dr. Michael Gannon (Consultant Obstetrician/Gynaecologist, Midlands Regional Hospital, Mullingar)
- Dr. Eoghan Mooney (Consultant Histopathologist, NMH & SVUH)
- Dr. Nadine Farah (Consultant Obstetrician/Gynaecologist, The Coombe Women’s Hospital & Tallaght Hospital)
- Dr. Una Fahy (Consultant Gynaecologist, ULH)

The GDG is also very grateful to Professor Michael Seckl and Professor Francois Golfier for sharing their expertise. We appreciate the time commitment that was involved in reviewing this guideline.

A log was recorded of all submissions and amendments from the National Stakeholder Review and International Expert Review Process.
Appendix 8: Implementation plan

The guideline implementation plan is based on the COM-B model of behaviour change (Michie et al., 2011). Changing clinical behaviour with clinical guidelines is more likely if the behaviour is specified in the implementation plan (Michie et al., 2004).

The Behaviour Change Wheel (Michie et al., 2011) was developed in 2011 as a tool for designing and evaluating behaviour change interventions. This model is based around the three conditions which influence behaviour: capability, opportunity and motivation. Each component can be mapped onto one of nine different intervention functions (education, training, enablement, persuasion, incentivisation, coercion, modelling, restrictions and environmental restructuring).

This model has been used to assess barriers and facilitators to guideline development and implementation and is outlined in detail in the NCCP Guideline Methodology Manual. Identification of barriers and facilitators is carried out during recommendations meetings with consultants and is recorded in the ‘considered judgement forms’.

The table below outlines the possible intervention functions for each recommendation in the guideline. Where the recommendation is already current practice, intervention functions are not required.
### Diagnosis

<table>
<thead>
<tr>
<th>Clinical questions</th>
<th>Recommendation</th>
<th>Facilitators/barriers to implementation</th>
<th>Target behaviour (B)</th>
<th>COM*</th>
<th>Possible intervention functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q2.2.1</strong> Should all women undergoing medical management of miscarriage have histopathology of products of conception to exclude trophoblastic disease?</td>
<td>The histological assessment of material obtained from the medical or surgical management of all failed pregnancies (if available) is recommended to exclude trophoblastic disease.</td>
<td>Current practice. (No additional intervention required). (Minimal impact on pathology).</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Q2.2.2</strong> For women with suspected molar pregnancy, what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?</td>
<td>Ultrasound examination is helpful in making pre-evacuation diagnosis but the definitive diagnosis is made by histological examination of the products of conception.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Q2.2.3</strong> For women where there is suspicion of partial or complete molar pregnancy who have an evacuation performed, in what time frame should the pathology report (post-evacuation) be available to the clinician?</td>
<td>It is recommended that in all cases of suspected molar pregnancy, the preliminary pathology report should ideally be available to the clinician within 14 days.</td>
<td>Protocols in relation to the management of laboratory tests from patients suspected of having GTD required - (prioritisation by histopathology attached to maternity hospitals in cases of suspected GTD).</td>
<td>Prioritisation in laboratories.</td>
<td>Motivation (Reflective) Opportunity (Physical) Education Persuasion, Enablement Environmental restructuring</td>
<td></td>
</tr>
</tbody>
</table>

**Capability** Psychological or physical ability to enact the behaviour.

**Opportunity** Physical and social environment that enables behaviour.

**Motivation** Reflective and automatic mechanisms that activate or inhibit behaviour.
<table>
<thead>
<tr>
<th>Clinical questions</th>
<th>Recommendation</th>
<th>Facilitators/barriers to implementation</th>
<th>Target behaviour (B)</th>
<th>COM*</th>
<th>Possible intervention functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2.2.4 For women with gestational trophoblastic disease should management be centralised to a specialised centre(s) to ensure optimum outcome?</td>
<td>The GDG recommends that a National GTD Registry, Monitoring and Advisory Centre should be established for all cases of GTD. The management of complicated cases should be discussed with the National GTD Registry, Monitoring and Advisory Centre’s clinical lead.</td>
<td>Lack of a National GTD Registry, Monitoring and Advisory Centre for GTD. Note: GTD Steering committee established (incl. representatives from all specialties and patient representatives). Treatment decisions to be monitored by national MDT, when established.</td>
<td>Resources required: - Staffing - Office - IT Registration of all cases.</td>
<td>Opportunity (Physical)</td>
<td>Training, Enablement, Environmental restructuring</td>
</tr>
<tr>
<td>Q2.2.5 For women with partial and complete molar pregnancy, what clinical and human chorionic gonadotropin monitoring protocol should be carried out to ensure they have been fully followed up and require no further therapy or monitoring?</td>
<td>For patients with complete hydatidiform mole serum hCG is monitored weekly (on the same hCG platform) until normalisation for three weeks. - If this occurs within eight weeks then monitor monthly for six months from the time of evacuation. - If normalisation occurs &gt;eight weeks post evacuation then monitoring continues monthly for six months post normalisation. For patients with partial hydatidiform mole the serum hCG should be monitored weekly until normalization and one further confirmatory hCG measurement is performed 4 weeks later. If that confirmatory hCG is normal then follow up is complete.</td>
<td>Current practice. Practical guidance for implementation - hCG levels should be measured on the same platform for the duration of monitoring. - Survey ongoing re: variation in platforms currently used.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Staging

<table>
<thead>
<tr>
<th>Clinical questions</th>
<th>Recommendation</th>
<th>Facilitators/barriers to implementation</th>
<th>Target behaviour (B)</th>
<th>COM*</th>
<th>Possible intervention functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q2.3.1</strong> For women with Gestational Trophoblastic Neoplasia (GTN), what investigations should be done to accurately stage GTN?</td>
<td>Women with malignant GTN should have hCG, pelvic ultrasound, CT scan of abdomen and pelvis, and a chest x-ray. If metastases are present on chest x-ray a CT scan of the thorax and an MRI of the brain should be performed.</td>
<td>Access to imaging / radiology services. Increased use of CT and US (small numbers ~25-30/yr).</td>
<td>Resources and training required (i.e. training &amp; proficiency in use of doppler US)</td>
<td>Capability (Physical) Opportunity (Physical)</td>
<td>Training, Enablement, Environmental restructuring</td>
</tr>
</tbody>
</table>

| **Q2.3.2** For women with gestational trophoblastic neoplasia (GTN), what risk scoring system should be used to stage GTN? | Women with GTN (invasive mole, choriocarcinoma) should be assigned a FIGO score to direct management decisions of chemotherapy regimens. | Current practice. Note: Staging will be carried out in conjunction with National MDT, when established. | Current practice. | N/A | N/A |

[63]
<table>
<thead>
<tr>
<th>Clinical questions</th>
<th>Recommendation</th>
<th>Facilitators/barriers to implementation</th>
<th>Target behaviour (B)</th>
<th>COM*</th>
<th>Possible intervention functions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q2.4.1</strong> For women with malignant gestational trophoblastic neoplasia, what are the clinical indicators to diagnose GTN warranting chemotherapy?</td>
<td>Indications for chemotherapy following diagnosis of GTN:  • Plateaued or rising hCG after evacuation,  • Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,  • Histological evidence of choriocarcinoma,  • Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of &gt; 2 cm on chest x-ray,  • Serum hCG of ≥20,000 IU/l more than four weeks after evacuation, because of the risk of uterine perforation,  • Raised hCG six months after evacuation even if still falling.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Q2.4.2</strong> For patients with low-risk (FIGO 0-6) GTN, what is the optimal first-line chemotherapy regimen?</td>
<td>Patients with a FIGO score of 0-6 can be treated with either single-agent methotrexate with or without folinic acid, or actinomycin D. In most European centres, methotrexate with folinic acid is preferred because it is less toxic than methotrexate alone or single-agent actinomycin D. Chemotherapy for low-risk disease should be continued for three cycles of maintenance treatment after hCG normalisation.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Q2.4.3</strong> For women with high-risk (FIGO ≥7) GTN what is the optimal first-line chemotherapy regimen?</td>
<td>Patients with a FIGO score of ≥7 should receive multi-agent chemotherapy and most centres now use EMA/CO, as it is highly effective, simple to administer and relatively non-toxic. Early deaths in ultra high-risk GTN can be reduced by induction therapy with etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EP/EMA.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical questions</td>
<td>Recommendation</td>
<td>Facilitators/barriers to implementation</td>
<td>Target behaviour (B)</td>
<td>COM*</td>
<td>Possible intervention functions</td>
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</tr>
<tr>
<td><strong>Q2.4.4</strong> For women with low-risk gestational trophoblastic neoplasia undergoing chemotherapy (first-course), what is the recommended course of action for observing and managing bleeding?</td>
<td>For women with low-risk GTN undergoing first-line chemotherapy, the first ± second course of chemotherapy should be administered as an in-patient at a centre with medical oncology, gynaecological services and interventional radiology.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| **Q2.4.5** For women with gestational trophoblastic neoplasia, what are the appropriate investigations to monitor response to chemotherapy and follow-up? | Monitoring during treatment low-risk: Patient should have human chorionic gonadotropin levels monitored twice a week during treatment.  
Monitoring during treatment high-risk: Patients with high-risk disease should have maintenance therapy for three cycles after hCG normalisation extended to four cycles for patients with poor prognostic features such as liver metastases with or without brain metastases.  
Follow-up post treatment: After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels.                                                                 | Current practice.                          | Current practice.   | N/A  | N/A                           |
<p>| <strong>Q2.4.6</strong> For women with low-risk gestational trophoblastic neoplasia what are the indicators to determine switching treatments from first-line chemotherapy? | For patients with low-risk GTN the clinical indicators for a change in treatment from first-line chemotherapy include: treatment related toxicity, a rise in hCG values over two successive measurements a week apart or a plateau in three successive weekly measurements a week apart.                                                                                      | Current practice.                          | Current practice.   | N/A  | N/A                           |
| <strong>Q2.4.7</strong> For women with low-risk gestational trophoblastic neoplasia who have not responded or have relapsed following normalisation of hCG after completion of single-agent treatment, what is the next line treatment? | For women with low-risk GTN who have not responded or have relapsed from single-agent treatment (methotrexate or actinomycin D), the next line of treatment is combination chemotherapy with EMA/CO.                                                                                                           | Current practice.                          | Current practice.   | N/A  | N/A                           |</p>
<table>
<thead>
<tr>
<th>Clinical questions</th>
<th>Recommendation</th>
<th>Facilitators/barriers to implementation</th>
<th>Target behaviour (B)</th>
<th>COM*</th>
<th>Possible intervention functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2.4.8 For women with high-risk GTN who have not responded or have relapsed from first-line treatment, what is second-line treatment?</td>
<td>For women with high-risk GTN who have not responded or have relapsed from first-line treatment, acceptable regimens include EP/EMA and TE/TP.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Q2.4.9 For women with GTN, who are acutely ill with liver, brain or lung metastasis at presentation, what is the optimum chemotherapy regimen?</td>
<td><strong>Emergency treatment</strong>  In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to BMA/CO or EP/EMA at a later point.  <strong>Hepatic metastases</strong>  In patients who are acutely unwell from liver disease emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. Patients with hepatic metastases at presentation should commence therapy using EP/EMA protocol.</td>
<td>Current practice.</td>
<td>Current practice.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical questions</td>
<td>Recommendation</td>
<td>Facilitators/barriers to implementation</td>
<td>Target behaviour (B)</td>
<td>COM*</td>
<td>Possible intervention functions</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td><strong>Cerebral metastases</strong>&lt;br&gt; In patients who are acutely unwell from CNS emergency chemotherapy can be started with two day EP, (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to high dose EMA/CO at a later point using an increased methotrexate dose (1gm/m²) combined with longer FA rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the hCG normalisation. In emergency situation with cerebral metastases, hi-dose dexamethasone is given followed by two day EP as above.</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic and synchronous cerebral metastases</strong>&lt;br&gt; In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP, (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. This combines the EMA (CNS) dose with the EP treatment. It misses out the day two of the normal EMA protocol as it is too myelosuppressive when combined with EP to allow for this.</td>
<td></td>
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</table>
Appendix 9: Summary of tools to assist in the implementation of the National Clinical Guideline


NCCP website. Information for Health Professionals and Patient Information

NCCP Chemotherapy Protocols

Health Information and Quality Authority (HIQA). National Standards for Safer Better Healthcare

Centre for Evidence Based Medicine

Improving Health: Changing Behaviour - NHS Health Trainer Handbook

UCL Centre for Behaviour Change


Appendix 10: Audit criteria

To ensure that this guideline positively impacts on patient care, it is important that implementation is audited. Audit is recommended to support continuous quality improvement in relation to the implementation of the National Clinical Guideline.

The management of trophoblastic disease in Ireland has been inconsistent due to a deficiency in expertise required to adequately monitor and treat patients with the disease. A National GTD Registry, Monitoring and Advisory Centre is currently being established in Cork University Maternity Hospital to register and audit all referrals. Following the diagnosis of molar pregnancy, all patients should be registered with the centre for serum hCG surveillance, initially on a weekly basis. The registration of patients (following patient consent) will allow centralised recording of hCG levels, which will ensure consistent monitoring and efficient management decisions, to improve clinical outcomes.

Protocols in relation to the information flow to the centre and patient booklets are being prepared. The centre will have a complete register of all cases of GTD in the Republic of Ireland. It will also allow for accurate comparison with international databases. The centre will convene a National MDT to advise on the management of all cases of GTN. Outcomes of incidence, efficiency of hCG monitoring and treatment outcomes in those requiring chemotherapy will form major components of national audit and allow international collaboration with other GTD registries worldwide both in terms of audit and future research.

It has been agreed by the HSE and the National Cancer Control Programme that all patients with molar pregnancy should be registered with the National Registry for hCG surveillance.

The need for careful follow-up of patients after molar pregnancy is generally accepted but it is known that follow-up may breakdown for a variety of reasons and when this happens persistent disease may prove difficult to manage. Evidence dictates that complex treatments are avoidable if specialist follow-up arrangements are sustained.

The purpose of registration of molar pregnancy is:

(i) To facilitate regular hCG follow-up.
(ii) To facilitate urgent management of patients requiring chemotherapy.

Registration applies to:

(a) Complete hydatidiform mole (classical type, androgenetic, no other fetal tissue).
(b) Partial hydatidiform mole (usually triploid, other fetal tissues present).
(c) Twin pregnancy with complete or partial hydatidiform mole.
(d) Limited macroscopic or microscopic molar change judged to require follow-up.

The referring consultant retains full responsibility for the patient and her follow-up care. The National Registry will provide the patient, the gynaecologist and the general practitioner with the results of the hCG follow up. The National Registry will also inform the patient of when samples are due and will send reminders if she defaults. Assays are usually done weekly until normal, then four-weekly until follow-up is complete.

The National GTD Registry, Monitoring and Advisory Centre consists of a Clinical Director, two Clinical Nurse Specialists (CNS) (2 x 0.5 WTE) and secretarial support (1 x WTE). The office is located in Cork University Maternity Hospital. The registry will have an operational database onto which every patients hCG will be entered on a weekly basis. When registered each patient will receive communication from the CNS regarding the diagnosis and follow-up required. On a daily basis the team will review each follow up hCG result and make a decision whether the disease resolution is continuing or whether the patient requires treatment. Every patient will be discussed at a bi-
weekly national MDT meeting held by teleconference. Therefore the management and follow up of every patient will be centralised to the national trophoblastic team for expert efficient care. As mentioned above the referring clinician will retain overall responsibility for the patient but the national multidisciplinary team will decide and advise on all aspects of patient care.

The National GTD Registry, Monitoring and Advisory team will audit and report annually according to the KPIs determined by the clinical governance group under the auspices of the NCCP. The registration of patients is voluntary on the part of the diagnosing clinician.
Appendix 11: Budget impact assessment

Key message
This review of the literature on the economic evaluation of the diagnosis, staging and treatment of patients with GTD and the budget impact analysis highlights potential economic consequences of the clinical guideline recommendations.

The report was compiled by:
Ms. Deirdre Faherty, Senior Research Officer (NCCP) and Ms. Louise Murphy, Research Officer (NCCP).

The following people are thanked for the input they contributed: Ms. Michelle O’Neill, Senior Health Economist (HIQA), Dr. Conor Teljeur, Senior Statistician (HIQA), Ms. Catherine Duffy, GTD Co-Project Manager (NCCP), Ms. Ruth Ryan, GTD Co-Project Manager (NCCP), and Mr. Brendan Leen, Regional Librarian (HSE South East).

Economic literature review
A systematic literature search was carried out to identify relevant economic literature in relation to GTD. It was undertaken using the same basic search terms as derived from the clinical literature review but with the SIGN economic filter applied. The literature sources searched and the specific literature search terms are specified in the search strategy (table 8).

The initial search results identified 30 studies, of which 28 were rejected as they were deemed not relevant (figure 6). The results of our search highlight the paucity of primary and secondary studies evaluating the cost effective management of GTD and the impact on resources in the health service. The two relevant results (table 9) included a study reporting on the economic analysis of first-line treatment for low-risk GTN (Shah et al., 2012) and a review examining the organisation and funding of patient care and follow-up (Savage et al., 2008). The study by Shah and colleagues was deemed to be of acceptable quality, however an article, specifying some costing data, by Savage and colleagues was not an economic evaluation.

A study by Shah et al. (2012) in the U.S. assessed the cost differences of three first-line treatment strategies (8-day methotrexate/folinic acid; weekly methotrexate; and pulsed actinomycin-D [act-D]), similar to the treatment of low-risk GTN in the Irish setting. Costs were examined from a societal perspective, including direct total treatment costs and indirect lost labour production costs, however costs from the payers perspective have been calculated for the purpose of this review. Eight-day methotrexate/folinic acid was the least expensive at $4,775* (€3,731 – 2015 figure), followed by pulsed act-D at $6,019* (€4,703 – 2015 figure). Weekly methotrexate was found to be the most expensive treatment strategy at $8,893* (€6,949 – 2015 figure).

* Societal cost element has been excluded to render it a payer perspective.

Given the similarities of the epidemiology, patient demography and treatment pathways, it is assumed that the results of UK studies will be broadly applicable to the Irish setting.

Savage et al. (2008) reviewed the organisational and clinical management components that contribute to achieving high cure rates among patients with low-risk Gestational Trophoblastic Tumour (GTT) at the UK National Trophoblastic Disease Centre at Charing Cross Hospital. The NHS budget for the Charing Cross GTT unit for the follow-up service and all treatment, including hCG tests, patient assessment, in-patient admission, scans, drugs, administration and medical staff salaries amounts to approximately €2.67 million (€2.54m – 2015 figure) per year (based on 1,200 patients with a molar pregnancy registered, and 120 treated for GTT annually). The total cost per patient treated in the UK is approximately €20,000 (€19,076 – 2015 figure).
Although differences in the study settings and cost data limit the transferability of the results, the main conclusion that the optimisation of care for women with low-risk GTT would be the development of national or regional publicly funded GTT services, is likely generalisable to the Irish healthcare setting.

Methods
The search strategy is based on the search used in the clinical literature review with the addition of a SIGN economic studies filter for Medline (table 8), including EBSCO Discovery, NHS Economic evaluation database, Cochrane Economic Evaluations, and Cochrane (full). The economic literature search was conducted in September 2014.

Costs have been complemented in brackets by euro estimates to correct for the exchange rate, purchasing power parity (PPP) between countries and health inflation as per the Health Information and Quality Authority’s Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies in Ireland (HIQA, 2014).

Despite the conversion of the reported costs to PPP-adjusted euro values it is also important to remember that there may still be a number of other factors which mean that costs from other countries are not necessarily directly applicable to the Irish setting. Similarly, some analyses are conducted from a societal perspective and may account for more benefits than are considered in Irish cost-effectiveness analyses (CEAs), which only account for costs to the health sector. Accordingly, the euro-adjusted costs reported here should only be considered broadly indicative rather than precisely adjusted estimates for the Irish health system.
### Table 8 Economic literature review protocol

<table>
<thead>
<tr>
<th>ID</th>
<th>Search</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>(MH &quot;Gestational Trophoblastic Disease&quot;)</td>
</tr>
<tr>
<td>S2</td>
<td>(MH &quot;Hydatidiform Mole&quot;)</td>
</tr>
<tr>
<td>S3</td>
<td>(MH &quot;Trophoblastic Neoplasms&quot;)</td>
</tr>
</tbody>
</table>
| S4 | TI "gestational trophoblastic neoplasms" OR AB "gestational trophoblastic neoplasms"
| S5 | TI "gestational trophoblastic disease OR AB "gestational trophoblastic disease"
| S6 | TI "invasive mole" OR "invasive mole"
| S7 | TI choriocarcinoma OR AB choriocarcinoma
| S8 | TI "gestational trophoblastic tumour" OR AB "gestational trophoblastic tumour"
| S9 | TI "hydatidiform mole" OR AB "hydatidiform mole"
| S10 | TI "persistent trophoblastic disease OR AB "persistent trophoblastic disease"
| S11 | (TI GTT OR GTD OR GTN) OR (AB GTT OR GTD OR GTN)
| S12 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
| S13 | (MH "Economics")
| S14 | (MH "Costs and Cost Analysis")
| S15 | (MH "Cost Allocation")
| S16 | (MH "Cost-Benefit Analysis")
| S17 | (MH "Cost Control")
| S18 | (MH "Cost Savings")
| S19 | (MH "Cost of Illness")
| S20 | (MH "Cost Sharing")
| S21 | (MH "Deductibles and Coinsurance")
| S22 | (MH "Health Care Costs")
| S23 | (MH "Direct Service Costs")
| S24 | (MH "Drug costs")
| S25 | (MH "Employer Health Costs")
| S26 | (MH "Hospital Costs")
| S27 | (MH "Health Expenditures")
| S28 | (MH "Capital Expenditures")
| S29 | (MH "Value of Life")
| S30 | (MH "Economics, Hospital")
| S31 | (MH "Economics, Medical")
| S32 | (MH "Economics, Nursing")
| S33 | (MH "Economics, Pharmaceutical")
| S34 | (MH "Fees and Charges")
| S35 | (MH "Budgets")
| S36 | low N2 cost*
| S37 | high N2 cost*
| S38 | (healthcare OR "health care") N2 cost*
| S39 | (TI fiscal OR funding OR financial OR finance) OR (AB fiscal OR funding OR financial OR finance)
| S40 | cost* N2 estimate
| S41 | cost* N2 variable
| S42 | unit N2 cost*
| S43 | (TI economic* OR pharmacoeconomic* OR price* OR pricing*) OR (AB economic* OR pharmacoeconomic* OR price OR pricing*)
| S44 | (MH "Medical Savings Accounts")
| S45 | S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44
| S46 | S12 AND S45
Figure 6 Economic literature review results

Identification

Records identified through database searching
(n = 30)

Screening

Records excluded* by screening of title and study type
(n=17)

Eligibility

Records screened
(n=13)

Included

Studies included in economic review
(n=2)

* Exclusion criteria
Not a cost effectiveness study
Not in English language
Not relevant to guideline recommendations
### Table 9 Economic literature evidence table

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Analysis Details</th>
<th>Costs</th>
<th>Results</th>
</tr>
</thead>
</table>
| Shah et al. (2012) | First-line low-risk GTN treatment strategies:  
- 8-day methotrexate/folinic acid  
- Weekly methotrexate  
- Pulsed actinomycin-D (act-D) | Country: USA  
Discount rate: none used as all costs are incurred within a year  
Perspective: societal  
Time Horizon: to patient cure, which depends on which first-line treatment is given (average of 7.9, 4.7 and 5.1 weeks for Weekly methotrexate, 8d methotrexate/folinic acid and Pulse actinomycin-D, respectively)  
Model type: decision tree implementation of a cost-minimisation analysis | 8-day methotrexate/folinic acid was found to be the least expensive to society, followed by pulsed act-D ($4,775 vs. $6,019 average cost from a payers perspective per cure, respectively), with act-D becoming more favourable only with act-D per cycle <$231, or response rate to first-line therapy >99%. Weekly methotrexate is the most expensive first-line treatment strategy ($8,893 average cost per cure), despite being least expensive to administer per cycle, based on lower first-line response rate. Absolute societal cost of each strategy is driven by the probability of needing expensive third-line multiagent chemotherapy, however relative cost differences are robust to sensitivity analysis over the reported range of cycle number and response rate for all therapies. |
| Savage et al. (2008) | Country: UK  
Perspective: NHS  
Discount rate: None  
Time Horizon: None  
Model type: None | The NHS budget for the Charing Cross GTT unit for the follow-up service and all treatment, including hCG tests, patient assessment, in-patient admission, scans, drugs, administration and medical staff salaries amounts to <£2 million ($4 million) per year. If the modest cost of the hCG follow-up service for the 90% of patients who do not require additional treatment, the costs amount to ~£15,000 ($30,000, €20,000) per patient treated. | In the UK system the total cost per patient treated is approximately £15,000. |
Budget impact of National Clinical Guideline

Scope of the budget-impact analysis
This guideline aims to consolidate and improve the quality of clinical practice regarding the diagnosis, staging, and treatment of patients with GTD. Recommendations deemed to be current practice have no additional resource implications, however recommendations involving a change in practice will incur costs.

The cost-impact analysis focused on the recommendations considered to require additional resources, as determined by the Guideline Development Group. Three such recommendations have been identified, however only one of these is considered to have a significant resource impact.

Recommendation 2.2.4.1
The guideline development group recommends that a National GTD Registry, Monitoring and Advisory Centre should be established for all cases of GTD.

This recommendation has the potential to identify the volume of patients with GTD in the country, as well as advising on optimal management pathways and auditing outcomes. In Ireland, data on incidence of GTD comes from the Hospital In-Patient Enquiry (HIPE) system. In 2013, there were 195 discharges to hospitals in the Irish public system. It is estimated that approximately 86 patients gave rise to the 195 discharges – this estimate is calculated by deduplicating discharges to hospital with the same medical record number. However, this estimate is likely to be an over estimate as the lack of a unique identifier makes tracking patients across hospitals impossible in the HIPE system. So any patient that was diagnosed in one hospital and later admitted to another is likely to be double counted. The National GTD Registry, Monitoring and Advisory Centre is currently in the process of being set up and protocols in relation to the information flow to the centre are being prepared.

A breakdown of costs to date in setting up a National GTD Registry, Monitoring and Advisory Centre are as follows:

<table>
<thead>
<tr>
<th>National GTD Centre</th>
<th>Set up costs (year 1)</th>
<th>Annual costs (year 2 onwards)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant session cost</td>
<td>-</td>
<td>€45,708</td>
</tr>
<tr>
<td>*Clinical Nurse Specialist (2 x 0.5 WTE)</td>
<td>€50,874</td>
<td>€50,874</td>
</tr>
<tr>
<td>*Clerical Officer (1 x WTE)</td>
<td>€28,626</td>
<td>€28,626</td>
</tr>
<tr>
<td>PC with internet access</td>
<td>€1,300</td>
<td>€500</td>
</tr>
<tr>
<td>Colour printer</td>
<td>€370</td>
<td>-</td>
</tr>
<tr>
<td>Printing cost</td>
<td>€500</td>
<td>€500</td>
</tr>
<tr>
<td>Telephone/fax</td>
<td>€500</td>
<td>€500</td>
</tr>
<tr>
<td>**Website</td>
<td>€6,000</td>
<td>€500</td>
</tr>
<tr>
<td>Database development fee</td>
<td>€7,040</td>
<td>-</td>
</tr>
<tr>
<td>Annual license/maintenance cost</td>
<td>€1,232</td>
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<tr>
<td>Teleconference phone (polygram)</td>
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<td>-</td>
</tr>
<tr>
<td>***Training &amp; education</td>
<td>€6,000</td>
<td>€6,000</td>
</tr>
<tr>
<td>Total</td>
<td>€107,442</td>
<td>€134,440</td>
</tr>
</tbody>
</table>

* Mid point of salary scale; ** Estimated cost; *** Staff education and training will be required and facilitated by the centre in Charing Cross Hospital
As mentioned previously, the NHS allocates the National Trophoblastic Disease Centre at Charing Cross Hospital a budget of approximately €2.54 million per year for the follow-up service and all treatment, including hCG tests, patient assessment, in-patient admission, scans, drugs, administration and medical staff salaries (based on 1,200 patients with a molar pregnancy registered, and 120 treated for GTT annually), which equates to a total cost of €19,076 per patient (Savage et al., 2008). The recommendation above however, only proposes the establishment of a National GTD Registry, Monitoring and Advisory Centre, which will not be responsible for follow-up and treatment.

**Recommendation 2.3.1.1**

Women with gestational trophoblastic neoplasia should have hCG, pelvic ultrasound, CT scan of abdomen and pelvis, and a chest x-ray.

There are resource implications in relation to recommending a CT versus a pelvic doppler ultrasound, however the number of patients requiring this is approximately 25-30 women per year. It is necessary to perform a pelvic ultrasound to rule out a new pregnancy as the cause of a plateau or rise in hCG level. If the ultrasound fails to demonstrate a new pregnancy, a CT scan of abdomen and pelvis should be performed to accurately stage GTN. Given the small number, any cost associated with this is likely to be an opportunity cost, it will be absorbed within current budgets and resources and will not need the purchase of additional equipment or the requirement for additional staff.

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic ultrasound</td>
<td>79.26</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>131.09</td>
</tr>
<tr>
<td>CT pelvis</td>
<td>131.09</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>41.91</td>
</tr>
<tr>
<td>Doppler ultrasound</td>
<td>78.26</td>
</tr>
</tbody>
</table>

(figures provided by St. James’s Hospital (SJH), Finance Department, 2015).

**Recommendation 2.2.3.1**

In all cases of suspected molar pregnancy, the preliminary pathology report should ideally be available to the clinician within 14 days.

This recommendation requires prioritisation by histopathology laboratories attached to maternity hospitals in cases of suspected GTD. The proposed recommendation focuses on timing and while the cost associated with expedited pathology reports is not expected to have any impact on resources, it may have an impact on hospitals who are currently overstretched.

**Relevance to the guideline recommendations**

In summary, the cost of establishing a National GTD Registry, Monitoring and Advisory Centre is estimated to be in the region of €107,000, and approximately €134,000 per year thereafter to maintain the centre. It will have the potential to identify the volume of patients with GTD in the country.

In addition, while there are resource implications in relation to recommending a CT versus a pelvic doppler ultrasound, given the small number, any cost associated with this is likely to be an opportunity cost, which will be absorbed within current budgets and resources.

Similarly, there is unlikely to be any substantial consequences for healthcare resources with requests for expedited pathology reports in cases of suspected molar pregnancy however it may have an impact on hospitals who are currently overstretched.
Appendix 12: Glossary of terms and abbreviations

Definitions within the context of this document

**Case control study**  The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. (CEBM website)

**Case series**  A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (NCI Dictionary)

**Choriocarcinoma**  A malignant disease characterised by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic villi, hemorrhage, and necrosis with direct invasion into the myometrium and vascular invasion resulting in spread to distant sites. (Lurain, 2010)

**Cohort study**  A research study that compares a particular outcome (such as lung cancer) in groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke compared with those who do not smoke). (NCI dictionary)

**Complete mole**  Complete moles are diploid and androgenic in origin, hydatidiform mole with no evidence of fetal tissue. Complete moles usually (75–80%) arise as a consequence of duplication of a single sperm following fertilisation of an ‘empty’ ovum. Some complete moles (20–25%) can arise after dispermic fertilisation of an ‘empty’ ovum. (RCOG, 2010)

**Epithelioid trophoblastic tumour (ETT)**  ETT is a rare variant of PSTT. It develops from neoplastic transformation of chorionic-type extra-villous trophoblast. ETT typically presents as a discrete, hemorrhagic, solid, and cystic lesion that is located either in the fundus, lower uterine segment, or endocervix. Like PSTT, it forms tumour nodules in the myometrium. (Berkowitz et al., 2015a)

**External validity**  The extent to which we can generalise the results of a study to the population of interest.

**Internal validity**  The extent to which a study properly measures what it is meant to measure.

**Invasive mole**  A benign tumour that arises from myometrial invasion of a hydatidiform mole via direct extension through tissue or venous channels. (Lurain, 2010)

**Meta-analysis**  A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself. (NCI dictionary)
| **Partial mole** | Partial moles are usually (90%) triploid in origin, with two sets of paternal haploid genes and one set of maternal haploid genes. Partial moles occur, in almost all cases, following dispermic fertilisation of an ovum. Ten percent of partial moles represent tetraploid or mosaic conceptions. In a partial mole, there is usually evidence of a fetus or fetal red blood cells. (RCOG, 2010) |
| **Placental site trophoblastic tumor** | PSTTs are malignant and develop from extravillous, intermediate trophoblast. They are usually diploid and monomorphic. Microscopically, these tumours show tumour (PSTT) no chorionic villi and are characterised by a proliferation of mononuclear intermediate trophoblast cells with oval nuclei and abundant eosinophilic cytoplasm. (Berkowitz et al., 2015a) |
| **Randomised trial** | An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. (CEBM website) |
| **Systematic review** | The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardised methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results. (CEBM website) |
Abbreviations

5-FU  5-Fluorouracil
ACT-D  Actinomycin-D
AGREE II  Appraisal of Guidelines for Research and Evaluation II
BH  Beaumont Hospital
CC  Choriocarcinoma
CEBM  Centre for Evidence-Based Medicine
CEO  Chief Executive Officer
CEA  Cost effectiveness analysis
CHAMOCA  Cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan and vincristine
CHM  Complete Hydatidiform Mole
CINAHL  Cumulative Index to Nursing and Allied Health Literature (database)
CNS  Central Nervous System
CO  Cyclophosphamide and vincristine
COM-B  Capability, Opportunity and Motivation Behaviour Model
CSF  Cerebral spinal fluid
CSO  Central Statistics Office
CT  Computed tomography
CUH  Cork University Hospital
CUMH  Cork University Maternity Hospital
CXR  Chest X-ray
DoHC  Department of Health and Children
DoH  Department of Health
EBP  Evidence-Based Practice
EBSCO  Elton Bryson Stephens COmpany (database)
EMA  Etoposide, methotrexate and actinomycin D
EMA/CO  Etoposide, methotrexate, actinomycin D plus cyclophosphamide and vincristine
EP  Etoposide and cisplatin
ESMO  European Society for Medical Oncology
ETT  Epithelioid trophoblastic tumour
FA  Folinic Acid
FAV  5-FU, actinomycin D, and vincristine
FBC  Full blood count
FIGO  International Federation of Gynecology and Obstetrics
GBP  Great British Pound
G-CSF  Granulocyte-colony stimulating factor
GDG  Guideline Development Group
GTD  Gestational Trophoblastic Disease
GTN  Gestational Trophoblastic Neoplasia
GTT  Gestational Trophoblastic Tumour
GUH  Galway University Hospital
hCG  Human Chorionic Gonadotropin
HIPE  Hospital In-Patient Enquiry
HIQA  Health Information and Quality Authority
HM  Hydatidiform Mole
HSE  Health Service Executive
ICGP  Irish College of General Practitioners
IM  Intramuscular
ISMO  Irish Society for Medical Oncologists
IT  Intrathecal
IV  Intravenous
KCl  Potassium chloride
LFT  Liver Function Test
MAC  Methotrexate, actinomycin D, cyclophosphamide or chlorambucil
MDT  MultiDisciplinary Team
MRC  Medical Research Council
MRI  Magnetic Resonance Imaging
NCCP National Cancer Control Programme
NETDC New England Trophoblastic Disease Centre
NHS  National Health Service
NMH  National Maternity Hospital
OS  Overall Survival
PET  Positron Emission Tomography
pGTN Persistent Gestational Trophoblastic Neoplasia
PHM  Partial hydatidiform mole
PICO Population/patient; intervention; comparison/control; outcome;
PICO(T) Population/patient; intervention; comparison/control; outcome; (time)
po  per oratum
PPP  Purchasing Power Parity
PSTT Placental site trophoblastic tumour
QUB Queen’s University Belfast
RCOG Royal College of Obstetricians and Gynaecologists
RCPI Royal College of Physicians of Ireland
RCSI Royal College of Surgeons in Ireland
RCT Randomised Controlled Trial
SFH  St. Francis Hospice
SJH  St. James’s Hospital
SLRON St. Lukes Radiation Oncology Network
SVUH St. Vincent’s University Hospital
TAP Thorax, abdomen and pelvis
TE/TP Paclitaxel/cisplatin and paclitaxel/etoposide
TVU Transvaginal ultrasound
U&E  Urea and electrolytes
ULH  University of Limerick Hospitals
US  Ultrasound
WHO  World Health Organisation
WRH  Waterford Regional Hospital
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(Background section)


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(Appendices)


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