

## Immunochemical Faecal Occult Blood Test (IFOBT) for Colorectal Cancer (CRC) Screening Executive Summary

[Adapted from the report by SYFUL AZLIE MD FUZI]

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2011

### Background

Colorectal cancer (CRC) is one of the most common forms of gastrointestinal (GI) cancer in the world today. It is the fourth most common form of cancer worldwide and the most frequent in North America, Australia, New Zealand, Argentina, and parts of Europe. According to the latest report of the National Cancer Registry (NCR) in Peninsular Malaysia 2006, CRC was the second most common cancer after breast cancer. It is the first among male and also second among female. The incidence of CRC has increased over the past decade. The age-standardised incidence rate (ASR) was estimated to be 8.1 per 100,000 population in 1987; 11.9 in 1998; and 13.9 in 2002; whereas it was 18.4 in 2006 in Peninsular Malaysia. Although high incidence of CRC was reported, there is no national CRC screening programme implemented. The diagnosis of CRC raises many questions and there is a need for clear, understandable answer, and the only contentious issue is which screening test to use. Therefore, the purpose of this Health Technology Assessment (HTA) on immunochemical faecal occult blood test (IFOBT) was to evaluate whether, and under what conditions, it would be effective, safe, and cost-effective tests for CRC screening among general population in Malaysia.

### Technical Features

Faecal occult blood refers to blood in the faeces that is not visibly apparent. A faecal occult blood test (FOBT) is designed to identify hidden or small quantities of blood in faecal sample. There are two main types of FOBTs: guaiac-based faecal occult blood test (gFOBT) and IFOBT which is also known as faecal immunochemical test (FIT). Guaiac-based test are the long established and most commonly used in the average risk population for CRC screening programme. However, a wide variety of newer commercially IFOBT are now available, either qualitative or quantitative test methods. The qualitative test method for IFOBT require minimal processing and involve developing a test strip with controls and reading a colour reaction while the quantitative method require more extensive laboratory processing which provide automated instrumental test development and reading with adjustable sensitivity threshold. The reference or gold standard for these tests is colonoscopy with biopsy.

### Policy Question

- i. Should IFOBT be used as a screening test for CRC screening in Malaysia?
- ii. Which test method for IFOBT is the most suitable to be used for CRC screening in Malaysia?

### Objective

- i. To assess the diagnostic accuracy of the various types of IFOBTs used for CRC screening among general population.
- ii. To assess the effectiveness of CRC screening using various types of IFOBT among general population compared to no screening.
- iii. To assess the safety of the various types of IFOBT used as a screening test for CRC.
- iv. To assess the economic implication of the various types IFOBTs used for CRC screening among general population.
- v. To assess whether CRC screening using various types of IFOBT have issues related to the ethical, legal, and organizational aspects.

### Methods

Electronic databases such as MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of

Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning database, INAHTA database, HTA database and FDA database were searched. No limits were applied to the search. Additional articles were identified from bibliographies of retrieved articles and hand-searching of journals. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force and NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4(2nd Edition), March 2001 for test accuracy studies.

## **Result and conclusion**

### **Diagnostic accuracy and effectiveness:**

There was fair level of evidence to suggest that the sensitivity and specificity of IFOBT varies with the cut-off points or positivity threshold of haemoglobin. The sensitivity of IFOBT (cut-off point between 100 ng/ml to 150 ng/ml) is around 89.0% for CRC whereas specificity around 97.0%. Positive predictive value (PPV) ranged from 4.0% to 34.0% for CRC and from 11.2% to 40.3% for high risk adenomas. False positive rate ranged from 1.5% to 6.0% for CRC. Immunochemical faecal occult blood test (IFOBT) identified small adenomas ( $\leq 9$  mm) with a level of sensitivity that was higher than the false positive rate (7.0% versus 4.5%,  $p < 0.001$ ).

Several studies have revealed that the diagnostic accuracy or performance of IFOBT was influenced by two important factors: high temperature and lag time before the faecal sample is analyzed because of haemoglobin stability. There was a significant difference in the proportion of IFOBT positive results in the summer than in winter as there was a significant fall in haemoglobin concentration at higher ambient temperatures. A recent study has reported that the performance of the IFOBT was decreased (occurrence of false negative results) by a delay in time between faecal sampling and laboratory delivery because of haemoglobin degradation.

A two-day faecal collection method was found to be more cost-effective compared to three-day faecal collection method for use in IFOBT as a means of screening for CRC.

A screening programme using IFOBT can be effective for prevention of advanced CRC (risk of developing advanced CRC was reduced from 28.0% to 46.0%) and reduced mortality from 23.0% to 60.0%. Regular IFOBT can detect precancerous lesions and CRC in early stages and thus reduce mortality from CRC.

### **Safety:**

There was no retrievable evidence on the safety of IFOBT for CRC screening. However, several test methods on IFOBT have United States Food & Drug Administration (US FDA) approval.

### **Economic evaluation**

There was evidence to suggest that IFOBT or FIT was cost-effective in comparison with no screening. The generated incremental cost-effectiveness ratios (ICERs) were USD\$905 and CAN\$611 per quality-adjusted life year in Taiwan and Canada, respectively. An economic evaluation in Canada also revealed that annual FIT with mid-range testing characteristics, was more effective and less costly compared to all strategies (including no screening). By using this modality, it was postulated that number of CRC could be reduced about 71.0% and the numbers of CRC deaths about 74.0%, while saving CAN\$68 per person. In the Malaysian context, the cost for qualitative IFOBT ranged from RM 3.50 to RM 7.50 per test.

### **Recommendation**

Based on the above review, evidence suggested that CRC screening using IFOBT can be considered for general population in Malaysia. Several randomised control trials (RCTs) and case-control studies had proven that CRC screening using FOBT can reduce CRC mortality. In countries like Taiwan and Canada had proven that FIT was cost-effective as compared with no screening.

However, organizational issues such as training, manpower, good referral centre or system, and funding as well as sample collection, storage condition, sample analysis, and transportation need to be addressed at all levels. Screening programme will need to consider methods which minimise the effect of high temperature and lag time before the faecal sample is analyzed. Considering all the factors that need to be addressed, therefore screening at a national level can be recommended only for the high risk individuals for both men and women beginning at age 50 years namely as follows:-

- i. Personal history of either polyps or colorectal cancer.
- ii. Family history of either polyps or colorectal cancer.
- iii. Personal history of inflammatory bowel disease.
- iv. Family history of cancer such as breast, uterine and ovarian.

Most of the available studies in the review indicated the use of quantitative IFOBT method required more extensive laboratory processing which provide automated instrumental test development and reading with adjustable positivity threshold or cut-off points. The use of fully automated IFOBT assay would be highly desirable in a national population based screening programme because of the large number of tests to be done and involving large number of laboratories. Automation allows time to be saved during development and could reduce the number of staff required to perform analysis, better standardization of results, and the application of very strict quality control criteria. However, one has to take cognizance of the staff with the skills required to use the automated equipment that they must be well trained. Hence, the use of quantitative IFOBT method can be recommended for CRC screening in Malaysia.

From the viewpoint of diagnostic validity and cost-effectiveness, the recommended cut-off points varied from 100 ng/ml to 150 ng/ml. A two-day faecal collection method was found to be more cost-effective compared to three-day faecal collection method for use in IFOBT as a means of screening for CRC.