Additional analysis to estimate the QALY loss that may be associated with missed high risk adenomas (HRAs) when FIT is compared with no triage.

Step 1. Exploration of base case results.

The base case results FIT vs. No test reported in the DAR Table 47 can be seen below:

	Incremental QALYs	Incremental cost (£)	ICER
HM-JACKarc vs. No test	0.0003	-£229	-£820,947*
OC-sensor vs. No test	-0.0001	-£259	£4,133,559

*HM-JACKarc dominates

In a first exploratory analysis we simply consider the base case costs fixed and calculate the reduction in QALYs so that the ICER is around £30,000 (in the SW quadrant of the CE-plane). For the OC-sensor this should be (approximately) -0.0086 and -0.0076 for the HM-JACKarc as shown in the table below.

	Incremental QALYs	Incremental cost (£)	ICER
HM-JACKarc vs. No test	-0.0076	-£229	£30,121
OC-sensor vs. No test	-0.0086	-£259	£30,145

This exploratory analysis can be used to indicate the approximate magnitude of the loss in QALYs needed to make FIT not cost-effective compared to no triage. A more detailed analysis is presented below.

Step 2. Estimate the effect of missed HRAs.

The main questions we want to answer are the following:

1) Estimate the effect of missing an HRA.
2) Estimate how many HRAs would be missed.
3) Determine whether FIT would still be cost-effective if these missed HRAs were counted.

The calculations below are for OC-sensor only since for the HM-JACKarc the sensitivity of detecting CRC is 100%. Moreover, when assumptions have been made, we have opted for a conservative approach. For example, we have assumed that missing an HRA patient would result in the same loss in QALYs as missing a CRC patient.

Table 48 in the DAR report shows that the QALYs accrued in the CRC Markov model are 0.0222 with no triage, which comes from 1.5% CRC prevalence, which means 0.0222/0.015 = 1.48 QALYs per CRC patient, and 0.0219 with the OC-sensor, which means 0.0219/0.015 = 1.46 QALYs per CRC patient. Thus, we consider for FIT a difference of -0.02 QALYs when compared to no triage due to missing a HRA/CRC patient. The number of missing HRA/CRC is given by 1-sensitivity = 7.9% for the OC-sensor (see Table 24 in the DAR), which implies a loss in QALYs of -0.02/7.9 = -0.0025 QALYs per % loss in sensitivity per CRC/HRA patient.

According to the DAR report, Table 8, we assumed that about 37% (1 - sensitivity) for detecting HRA/CRC will be missed, which implies -0.0025*37 = -0.0925 QALYs per CRC/HRA patient (assuming loss in QALY is same for HRAs). This is a conservative assumption, since according to the DAR report, page 58, it could also be assumed that about 16% (instead of 37%) will be missed.

Thus, at a prevalence of HRA plus CRC of 11.5% (the highest prevalence reported - page 56 in the DAR report), we have a loss in QALYs equal to -0.0925*0.0115 = -0.01 QALYs per tested patient.

We also know that missing some CRC patients would decrease cost. In the DAR report, Table 48, we can observe that the CRC costs are £19.48 for no triage (thus £19.48/0.015= £1299 per CRC patient) and £19.26 for the OC-sensor (£1284 per CRC patient). Thus, a difference of £15, which implies a decrease of £15/7.9% = £1.90 per % loss in sensitivity. Therefore, assuming a 37% (1 - sensitivity) loss, that would imply 37*11.5%*£1.90 = -£8.08 per tested patient.

The estimated new incremental values are then:

Incremental QALYs = -0.001+ (-0.01- (0.0219-0.0222)) = -0.0107

Incremental cost = -£259.25 + (-8.08- (19.26-19.48)) = -£251.39

ICER = £23,494

Where *new incremental value = original total + (new CRC increment -old CRC increment),* original total in the DAR report, Table 47, and old CRC increment in the DAR report, Table 48. Note that this ICER is in the SW quadrant and that makes the OC-sensor not cost-effective compared to no triage.

It should be emphasized that the calculations above assume that:

1) the QALYs lost due to missed HRA is the same as CRC,
2) the number of missing HRA/CRC (37%) is high and
3) the prevalence of both CRC/HRA is high.

For example, if we simply assume that half of the HRAs will go to CRC (which might still be seen as high) then we would essentially have a prevalence of about 6.5%. Following the calculations above, that would imply 0.006 QALYs lost per tested patient and increase in cost of £4.57 per tested patient.

The estimated new incremental values would be then:

Incremental QALYs = -0.001 + 0.0003-0.006 = -0.0067

Incremental cost = -£259.25 + 0.22-4.57 = -£254.90

ICER = £38,045

Thus, even if it is assumed that there is prevalence as high as 11.5% for CRC and HRAs and that half of all HRAs convert basically immediately to CRC then the OC-sensor would still be cost-effective.

Step 3. Additional exploratory scenarios.

Running the model with the sensitivity and specificity in the DAR report, Table 8 for the OC-sensor (and 1.5% prevalence) results in an ICER OC-sensor vs. No test = £178,448 in the SW quadrant, so the OC-sensor is still cost-effective. Increasing the prevalence to 11.5%, the ICER is £18,983 in the SW quadrant of the CE-plane (incremental QALYs -0.013). Therefore, the OC-sensor is not cost-effective. This is similar to the £23,494 reported above. However, this value is obtained is assuming the same loss in QALYs for HRA and CRC and no difference in costs.

Step 4. Conclusion.

The results of the additional analyses performed above seems to suggest that there would have to be a large loss in QALYs (compared to the base case incremental QALYs) due to missing HRA to make FIT not cost-effective compared to no triage.