**OPERA Ursodeoxycholic Acid Response Calculator**

***Guidance Notes version 3.0 dated 08 AUG 2023***

The Ursodeoxycholic Acid Response Score (URS) is a fully validated score which is accurate in predicting the likelihood that a primary biliary cholangitis (PBC) patient starting standard first line therapy with ursodeoxycholic acid (UDCA) will respond to that therapy. We have adapted the calculator to function in a specific way for the OPERA trial

In the version of the calculator to be used in the OPERA trial; response is defined as **normalisation of liver function tests**. The probability value given by the calculator is therefore the probability of liver function tests returning to normal after a year of UDCA therapy.

It is important that it is the **OPERA URS Calculator** version of the calculator that is used in the OPERA trial because other versions will use the probability of achieving other levels of liver function test improvement rather than normalisation as the readout.

Disclaimer: As the OPERA URS calculator gives results in terms of the probability of UDCA remission, it should not be used as a stand-alone clinical decision making tool, but rather as an adjunct to clinical decision making about patient care in PBC.

The OPERA trial is exploring the first line use of Obeticholic Acid (in combination with standard of care use of UDCA) in PBC patients with a **greater than 20% chance at disease outset of NOT normalising their liver function tests with UDCA**. The OPERA URS Calculator therefore plays an integral role in determining eligibility for the trial.

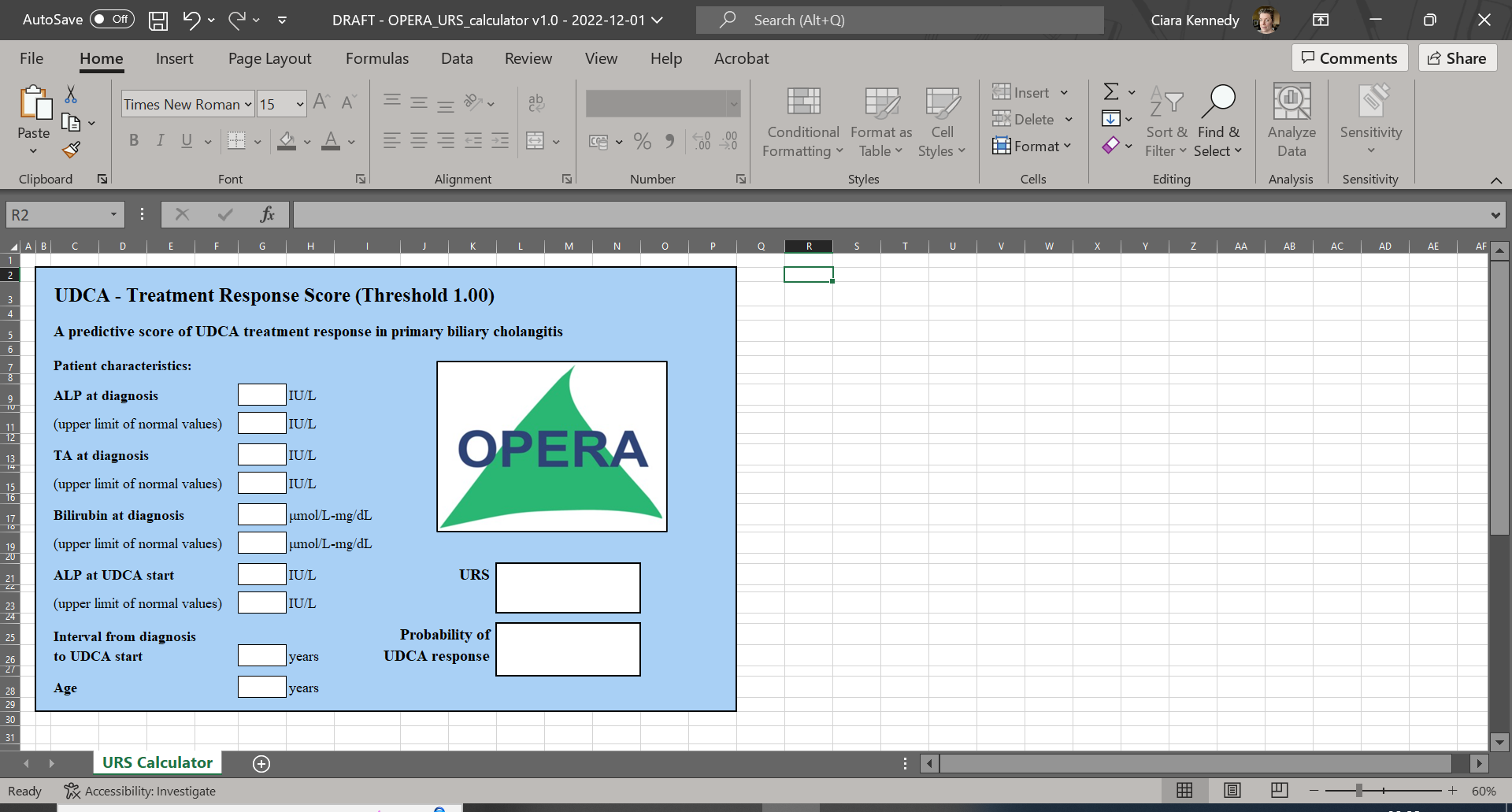


Fig 1. OPERA URS Calculator

***Using the OPERA URS Calculator in Practice*:** The calculator has been designed to be simple to use in practice. All the laboratory values to be entered will need to have the relevant local lab upper limit of normal (ULN) value entered alongside the patient value. This is because different NHS Trusts may have slightly different ULN values. The following values are entered into the calculator

***1)* *ALP at Diagnosis***: This is the value of alkaline phosphatase that was seen on the set of blood tests where PBC was first diagnosed. There has always been a time-lag between diagnosis and treatment commencement in PBC. This is the value at the first key time point in the disease which is the diagnosis.

***2) TA at Diagnosis:***This is the value for the transaminase (ALT or AST, whichever the local lab uses) at the point of diagnosis (i.e., the same time point as the alkaline phosphatase value in 1)

***3) Bilirubin at Diagnosis:***The bilirubin value at the same time as the values for 1) and 2)

***4) ALP at UDCA Start:***Where the URS is used in clinical practice this would be the alkaline phosphatase value at the point of UDCA commencement. In OPERA the participants will fall into one of two groups.

1. For people who are starting UDCA at the same time point as entering the trial. In this setting the “ALP at UDCA start” will be the alkaline phosphatase value at trial screening.
2. For people who have been on UDCA for a short period of time before enrolling in the trial. In this group the “ALP at UDCA start” is exactly that**, the alkaline phosphatase value at the date of UDCA commencement**.

***5) Interval from diagnosis to UDCA start:***This is the time (in years) between the date of diagnosis and the date on which UDCA is started. For ease we have included a date calculator in yellow to the right of the main URS calculator (Fig 2.). Date 1 = Date of diagnosis, Date 2 = Date of UCDA start.

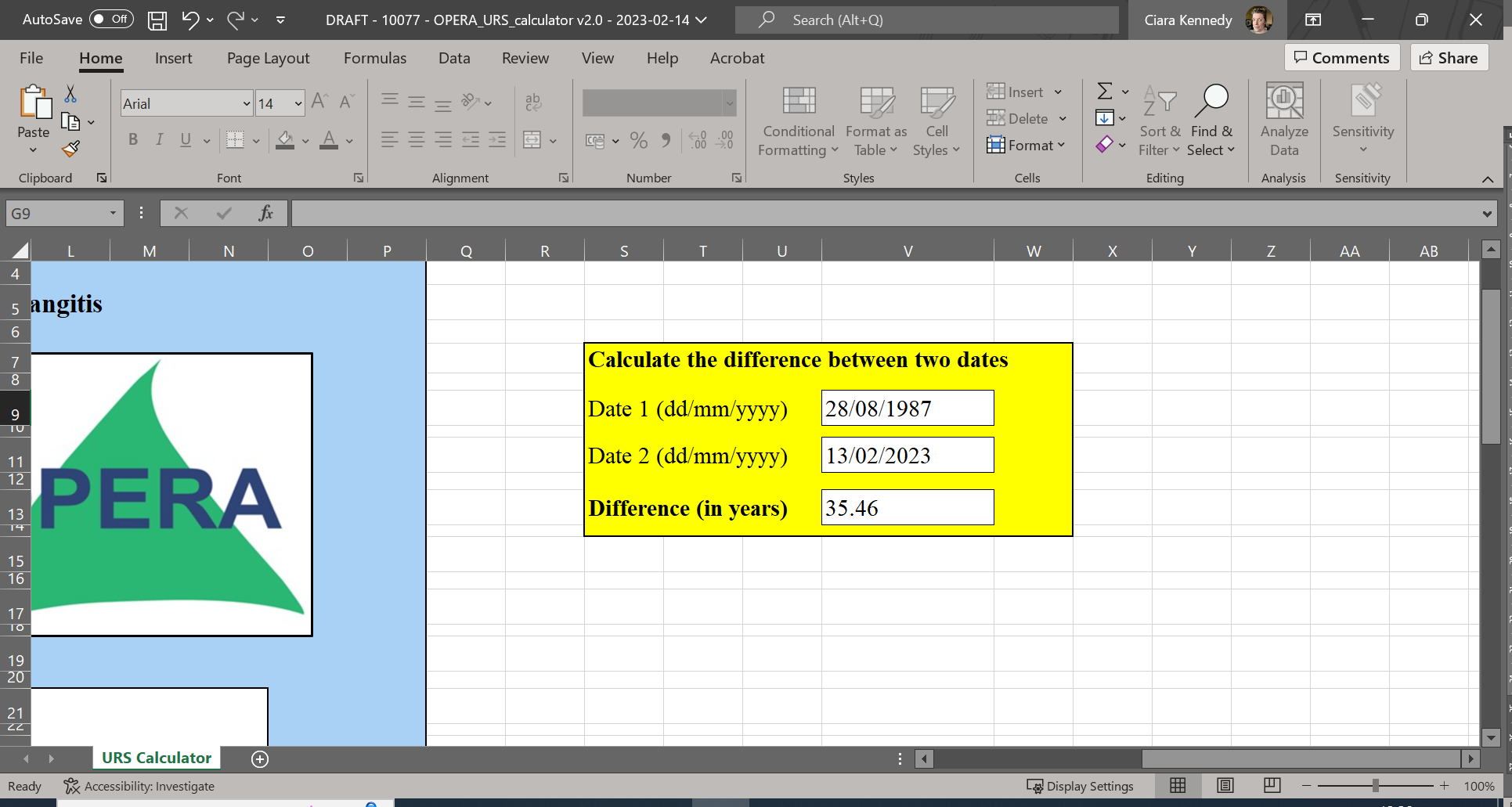


Fig 2. Interval from diagnosis to UDCA start calculator.

There are three groups:

1. For people who start UDCA at the beginning of the trial the date for UDCA start is the trial screening date.
2. For people who have already been on UDCA for a short period of time prior to screening it is the actual date they started UDCA. Please note the OPERA inclusion criterion 4. *Use of UDCA for <3 months at the time of consent*
3. People who have not yet started UDCA. For this cohort you do not need to use the Interval of diagnosis calculator (yellow). In this case please enter the value ‘0’ (zero) into the ‘Interval from diagnosis to UDCA start’ box.

**Note that** **this value must be the actual interval, not just round number of years** (for example if the interval is 4 years and 3 months the value entered should be 4.25, not 4).

***6) Age*:** This value is either

1. the age of the person in years at screening for the trial (if starting UDCA at that point)
2. or at the point of actual UDCA commencement if they have already started.

Again, this needs to be an exact value (i.e., someone who is 65 and 9 months the value entered is 65.75 not 65)

**Result:** Once all the data has been entered, the OPERA URS calculator will give two values:

1. The URS value is the technical score value.
2. Probability of UDCA response value

The key value is the “probability of UDCA response” value. This is the likelihood of UDCA response expressed as a probability.

**Eligibility for OPERA requires a value of 0.8 or less (i.e., an 80% or less chance of responding).**

Please ensure that you note the URS value and the Probability of UDCA Response values in the participant medical record and on the OPERA Screening and Recruitment Log and in the eCRF (Sealed Envelope).