<b>Purpose:</b> To develop and validate a regularization approach of optimizing B<sub>1</sub>-insensitivity of the quantitative magnetization transfer (qMT) pool-size ratio (F).

<b>Theory and Methods:</b> An expression describing the impact of B<sub>1</sub>-inaccuracies on qMT fitting parameters was derived using a sensitivity analysis. To simultaneously optimize for robustness against noise and B<sub>1</sub>-inaccuracies, the optimization condition was defined as the Cramér-Rao lower bound (CRLB) regularized by the B<sub>1</sub>-sensitivity expression for the parameter-of-interest (F). qMT protocols were iteratively optimized from an initial search space, with and without B<sub>1</sub>-regularization. Three 10-point qMT protocols (Uniform, CRLB, CRLB+B<sub>1</sub>-regulatization) were compared using Monte Carlo simulations for a wide range of conditions (SNR, B<sub>1</sub>-inaccuracies, tissues).

<b>Results:</b> The B<sub>1</sub>-regularized CRLB optimization protocol resulted in the best robustness of F against B<sub>1</sub>-errors, for a wide range of SNR and for both white and grey matter tissues. For SNR = 100, this protocol resulted in errors of less than 1% in mean F values for B<sub>1</sub>-errors ranging between -10 to 20%, the range of B<sub>1</sub> values typically observed in vivo in the human head at field strengths of 3 T and less. Both CRLB-optimized protocols resulted in the lowest σ<sub>F</sub> values for all SNRs, and did not increase in the presence of B<sub>1</sub>-inaccuracies.

<b>Conclusion:</b> This work demonstrates a regularized optimization approach for improving the robustness of auxiliary measurements (e.g. B<sub>1</sub>) sensitivity of qMT parameters, particularly the pool-size ratio (F). Predicting substantially less B<sub>1</sub>-sensitivity using protocols optimized with this method, B<sub>1</sub> mapping could even be omitted for qMT studies primarily interested in F.