In response to the comments made, we made the following changes.

Reviewer 1:

1. The statement in the Abstract that PCSs enable highly accurate structure determinations is somewhat overoptimistic. It is difficult to determine protein structures from PCS alone, in particular if the paramagnetic centers are in flexible tags.

Response:
We amended the second part of the sentence in the abstract:
"and PCSs generated from multiple tagging sites have been shown to enable highly accurate structure determinations at specific sites of interest even when using flexible tags, provided the fitted effective DeltaChi tensors accurately back-calculate the experimental PCSs measured in the immediate vicinity of the site of interest."

2. Mathematical notion is somewhat non-standard. There is no summation index in Eq. 2.

3. The (finite) volume element in Eq. 3 is called dV, which is normally the symbol for an infinitesimal volume element. It would be better to call it Delta-V to make it clear that it is of finite size.

4. Using the gradient symbol for the scalar quantities defined in Eqs. 6 and 7 is an unusual notation.

5. It might be useful to point out that the term that is summed in Eq. 6 corresponds to $|\cos(\tau_{ij})|$, where τ_{ij} is the angle between the vectors v_i and v_j. The quantity on the left hand side should carry an index j. Since the sum is over all i different from j, the normalization factor should be $n - 1$ instead of n.

6. The same applies to Eq. 7, where the term that is summed corresponds to $|\sin(\tau_{ij})|\,|v_i|\,|v_j|$. In general, I find the localization space volume of Eq. 3 to be the quantity with the most straightforward interpretation.

7. In the caption of Fig. 2, it would be informative to report the DeltaV value that corresponds to the given parameters.

Response: We implemented all changes as recommended in points 2-7.

Reviewer 2:
1) "The results indicate that the number of tags is much more important than the number of tagging sites. … I don't see that the claim of the abstract is supported by the data."

Response: We now clarify this in an additional point inserted at line 164: "(ii) In general, using more tags is of greater benefit than using more tagging sites. This is evidenced by

consistently smaller RMSD volumes associated with, e.g., the 95th percentile when using n+1 rather than n tags. (iii)…" In addition, we changed 'much more' in the abstract to 'more'.

2) "The distribution of the magnitude observed PCSs for a given tag / protein conjugate is not a Gauss distribution, but rather characterized by a few large, some intermediate and many small experimental PCSs. I, therefore, wonder whether the RMSD is really the most suitable criterion for the assessment, or if the normalised q-factor would be more suitable."

Response:
If a nuclear spin is located near the PCS isosurface, where the PCS is zero (i.e. the sign of the PCS changes), the Q-factor would involve division by a small number although this isosurface defines the location of the spin with maximum precision. Therefore, a Q-factor calculation would give a misleading impression of the uncertainty. By calculating the RMSD in ppm, it can be compared directly with the uncertainty of PCS measurements (which also is in ppm).

3) "In figure 6 it seems, as if the ubiquitin structure is for all panels A-D depicted in an identical orientation. If this is the case, it should be mentioned in the caption – if not – then figure 6 should be modified accordingly."

Response:
All panels of Figure 6 indeed show the protein in the same orientation. This is now spelled out in the figure legend.

4) "It is not entirely clear to me, if experimental noise on PCS has been considered in the simulation. It seems likely that noise would affect the one site / multiple tags scenario differently as the multiple sites / one tag, because the S/N ratio of PCS decreases with increasing SoI-metal distance and the coverage by several sites may compensate this to a certain extent."

Response:
The simulations are based on random tensor orientations. As tensors were not fitted using PCSs, the tensor orientations did not vary in response to PCS uncertainties. Furthermore, the simulations were for tensors that all have their origin at the same distance from the site of interest. If the tensor origins are at different distances from the site of interest (which is much more likely in the case of multiple than single tagging sites), smaller PCSs from more remote tensors will indeed be associated with larger relative errors. Importantly, however, the absolute uncertainty remains unchanged as far as it results from measuring the PCS as the difference between two chemical shifts. This uncertainty is well captured by the PCS RMSD (in ppm) we used to define the boundary of the localisation space.

In addition, we amended some minor issues we came across ourselves:
Line 37-38: included Pearce et al. 2017 and Orton et al., 2022 in the references
Line 59: removed '(measured in ppm)', as the PCS is dimensionless
Line 307: replaced 'For example' by 'As mentioned above'

Line 315: wrote Pearce with a capital
Line 320: replaced Herath et al., 2021 by Orton et al., 2022.